

Université de Montréal

**Synthesis of 1,2-methano-tetrahydrofuran derivatives and
1',2'-methano-2',3'-dideoxynucleosides as potential
antivirals**

par

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Résumé

En partant de la (*S*)-4-hydroxyméthyl-butyrolactone, commerciale et largement utilisée, la synthèse stéréocontrôlée de composés reliés de 1,2-méthano-1-substitué-4-hydroxyméthyl-tétrahydrofuranes a été réalisée en utilisant une stratégie de cyclopropanation publiée par le groupe du Professeur Hanessian. Dans le cadre d'une collaboration avec le SGC de Toronto, certains 1,2-méthano-1,4-tétrahydrofuranes substitués ont été testés contre un panel d'histone-méthyl-transférases.

Dans le second chapitre, une courte synthèse de trois analogues nucléosidiques contraints, 1',2'-méthano-2',3'-désoxypseudouridine (*C*-nucléoside), le 1',2'-méthano-2',3'-désoxyuridine et le 1',2'-méthano-2',3'-désoxycytidine et leur pro-médicament aryloxyphosphoramidate correspondant a été réalisée en utilisant la stratégie de cyclopropanation. Les tests biologiques de ces analogues modifiés en tant qu'agents antiviraux ont été effectués par les laboratoires Merck à Rahway, NY. USA. Aucun des composés n'a montré d'activité contre le VIH, le VRS et l'Herpès.

Mots-clés: cyclopropanation à l'étain, analogues nucléosidiques, phosphoramidates, activité antivirale, 1,2-méthano-1-substitué-4-hydroxyméthyl-tétrahydrofuranes, 1',2'-méthano-2',3'-désoxyuridine, nucléosides contraints.

Abstract

Starting from the commercially available and widely used (*S*)-4-hydroxymethyl- butyrolactone, the stereocontrolled synthesis of bicyclic 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofurans was accomplished using a tin-mediated cyclopropanation strategy reported by the Hanessian group. As a part of a collaboration with the SGC of Toronto, some of the 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofurans were tested against a panel of histone methyltransferases.

In the second chapter, a short synthesis of three constrained nucleosides analogues, 1',2'-methano-2',3'-dideoxypseudouridine (*C*-nucleoside); 1',2'-methano-2',3'-dideoxyuridine and 1',2'-methano-2',3'-dideoxycytidine and their corresponding aryloxyphosphoramidate-prodrugs was achieved using the tin-mediated cyclopropanation strategy. The biological testing of the modified analogues as antiviral agents was performed by Merck in Rahway, NY, USA. None of the compounds showed activity against HIV, RSV and Herpes.

Keywords: Tin-mediated cyclopropanation, nucleosides analogues, phosphoramidates, antiviral agents, 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofurans, 1',2'-methano-2',3'-dideoxyuridine, constrained nucleosides.

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Abbreviations list

ACC: 1-aminocyclopropanecarboxylic acid

AZT: Azidothymidine

BOX: bis(oxazoline)

CBz: Benzyloxycarbonyl

CMV: Cytomegalovirus

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM: Dichloromethane

dd: Doublet of doublets

ddd: Doublet of doublet of doublets

DIBAL-H: Diisobutylaluminum hydride

DNA: Deoxyribonucleic acid

DP: Diphosphate

DPPA: Diphenylphosphoryl azide

dt: Doublet of triplets

EBV: Epstein-Barr Virus

ESI: Electrospray ionization

EtOAc: Ethyl acetate

FDA: Food and Drug Administration (U.S.)

GFP: Green fluorescent protein

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIV: Human immunodeficiency virus

HRMS: High Resolution Mass Spectrometry

HSV1: Herpes simplex virus type 1-oral

HSV2: Herpes simplex virus type 2-oral

LiHMDS: Lithium bis(trimethylsilyl)amide

m: Multiplet

MeCN: Acetonitrile

MP: Monophosphate

NMR: Nuclear magnetic resonance

PPTS: Pyridinium *p*-toluenesulfonate

RNA: Ribonucleic acid

s: singlet

SGC: Structural Genomics Consortium

t: triplet

TBAF: Tetrabutylammonium fluoride

TBDPSCl: Tert-butyl(chloro)diphenylsilane

TBS: Tert-Butyldimethylsilyl

TDF: Tenofovir Disoproxil Fumarate

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

TLC: Thin-layer chromatography

TP: Triphosphate

UV: Ultraviolet

VZV: Varicella zoster virus

To my mom and brother

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1 Chapter 1: Synthesis of 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofurans

1.1 Introduction

The cyclopropane ring is a widespread subunit present in a variety of natural compounds such as terpenes pheromones, amino acids, and fatty acids.^{1,2} Some of the natural compounds containing the cyclopropane ring have shown antifungal, antiviral, anticancer, antimicrobial and antiestrogenic activities, with potential applications in modern medical treatments.³ In 1924 Staudinger and Ruzicka isolated and characterized (+)-*trans*-chrysanthemic acid **I** from the petals of pyrethrum flowers (Figure 1), which was found to act as an insecticide.^{2,4,5} The ester derivatives of **I** also known as pyrethroids, constitute one of the most utilized household insecticides.⁵

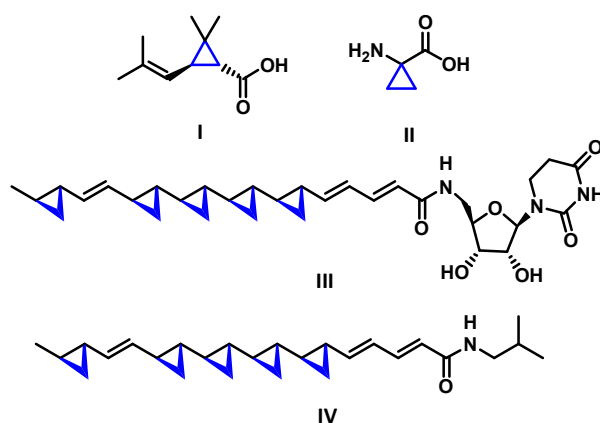


Figure 1 .Biologically active cyclopropane compounds from nature

1-Aminocyclopropanecarboxylic acid (ACC) **II** is another example of an important natural product containing a cyclopropane ring.⁶ It is the direct precursor to the plant hormone ethylene found in every green plant.⁷ In 1990 Yoshida et al.⁸ isolated a potent antifungal compound FR-900848 **III** from the fermentation broth of *Streptoverticillium fervens*. The compound is a nucleoside-fatty acid consisting of a uridine base linked to a monounsaturated fatty acid

containing five cyclopropane rings. Surprisingly, compound **III** is not an unique motif, Chemists at UpJhon Laboratories reported a similar natural product denominated U-106305 **IV** which acts as a cholesterol esterase inhibitor.^{9, 10}

A large number of natural compounds and their derivatives containing a cyclopropyl moiety have been synthesized and progressively incorporated into pharmaceuticals. The feature can be observed in the yearly list of the US FDA approved drugs:³ Ciprofloxacin¹¹ a broad spectrum antibiotic,¹² Saxagliptin an orally active hypoglycemic drug (anti-diabetic drug),^{13,14} Drospirinone¹⁵ a progestin used in birth control pills and Simeprevir a medication used in combination with other medications for the treatment of hepatitis C (Figure 2). Currently, Ciprofloxacin is on the World Health Organization's List of Essential Medicines.

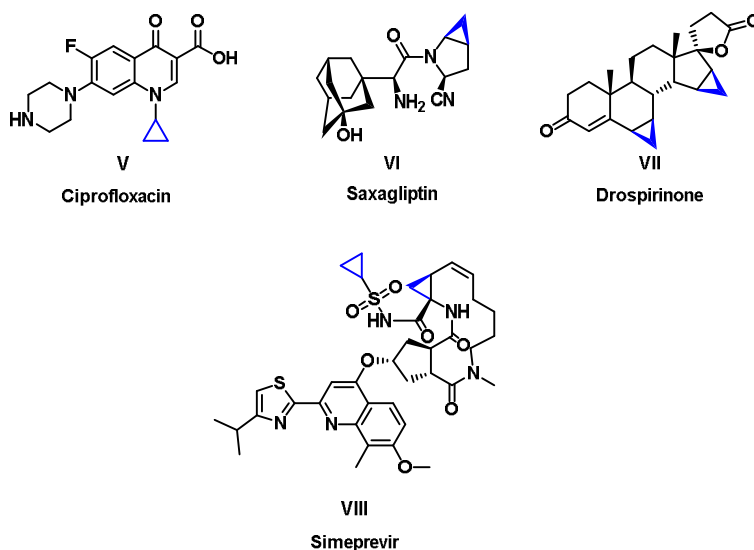


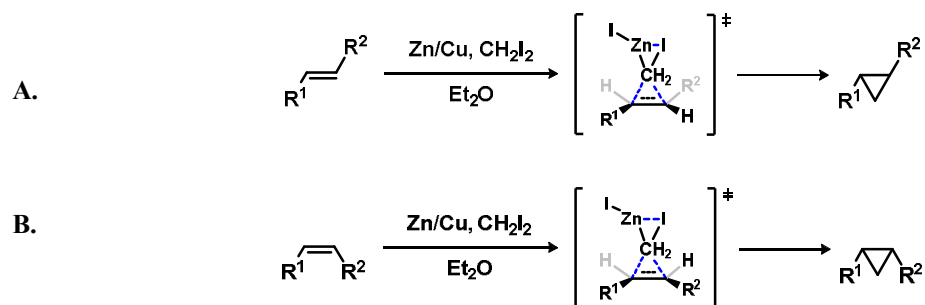
Figure 2. Drugs containing a cyclopropane ring.

Organic chemists have been always interested in finding novel methodologies to build the cyclopropane ring due to its structural properties, inherent strain, and reactivity. Currently, there are three general methods to synthesize cyclopropanes.^{1,16}

1.2 General methods of cyclopropanation

1.2.1 Simmons-Smith cyclopropanation via halomethyl method (Zn, Sm, Al)

In 1929 Emshwiller reported that iodomethyl zinc species can be obtained by the reaction of diiodomethane and Zn.¹⁷ Later studies by Simmons and Smith reported that the iodomethyl-zinc species can react with alkenes to form cyclopropanes.¹⁸ The method, recognized now as the Simmons-Smith cyclopropanation, is well-known for being stereospecific with respect to alkene geometry. In general, the method is compatible with a variety of functional groups. It has been proposed that the reaction proceeds through a concerted ‘butterfly-type’ transition state (Scheme 1) in a giving the substituted *cis* or *trans* cyclopropane.^{1,16}

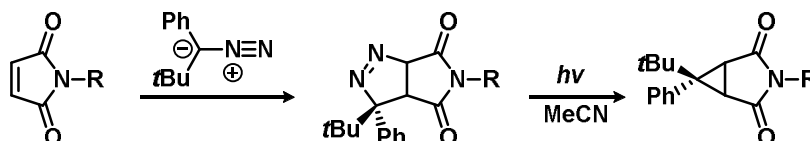


Scheme 1. Simmons-Smith cyclopropanation

Several modifications of the Simmons Smith method have been reported, starting with the use of diethyl zinc by Furukawa in 1967,¹⁹ to the modification of the nature of the metal or the design of chiral auxiliaries for asymmetric cyclopropanation. In an effort to achieve enantioselective cyclopropanation, Yamamoto, reported a variation involving the treatment of the olefin with different trialkylaluminiums and alkylidene iodide, exhibiting a great selectivity in the cyclopropanation of cyclic and acyclic substrates.²⁰ Some years later Molander described the use of samarium/mercury amalgam instead of zinc to generate samarium carbenoids.²¹ In 1994 an effective chiral controller was developed by Charette for the conversion of allylic alcohols into the corresponding enantiomerically enriched cyclopropanes using the Simmons-Smith type reaction.²²

1.2.2 Via decomposition of pyrazolines

The Δ^2 pyrazolines are widely used for the cyclopropanation of alkenes.^{23,24,25} Reaction of a diazocompound with an alkene via 1,3-dipolar cycloaddition produces a pyrazoline that can be isolated in some cases (Scheme 2).²⁶ When exposed to heat or light, pyrazolines rapidly form the cyclopropane ring with extrusion of nitrogen.



Scheme 2. Formation of cyclopropanes mediated by decomposition of pyrazolines

1.2.3 Via carbenes generated by decomposition of diazo compounds

Metal-mediated decomposition of diazo compounds is one of the most common methods for the synthesis of cyclopropanes. Among the most used diazo compounds are those bearing an electron-withdrawing group, such as phosphate esters,²⁷ nitro,²⁸ cyano and carboxylates.²⁹ The reaction proceeds via a Fisher type metal-carbene in a concerted asynchronous pathway in the transference of the methylene to the alkene (Figure 3).

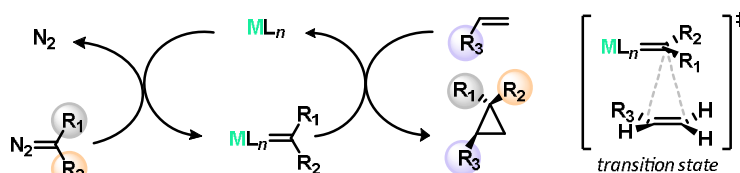


Figure 3. Fisher type metal-carbene

Several transition metals such as Cu, Ru and Rh can perform the diazo decomposition reaction. Highly diastereoselective catalytic copper-based cyclopropanation has been extensively studied and applied to a wide group of substrates. Since the original report by Masamune,³⁰ the use of bis(oxazoline) ligands, usually known as BOX ligands, with high enantiomeric purity has emerged as one of the most versatile systems for the cyclopropanation of alkenes. Some examples are presented in the Figure 4.

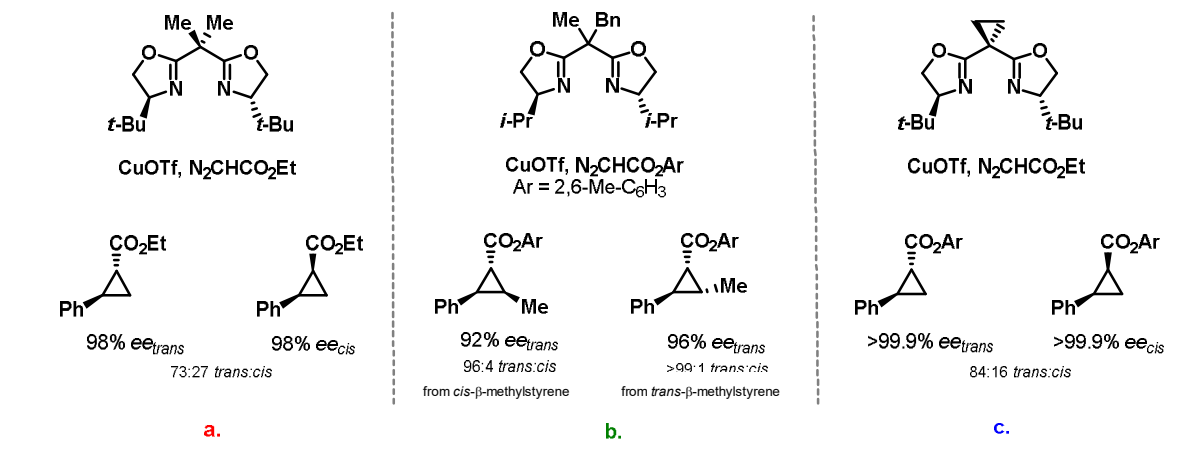
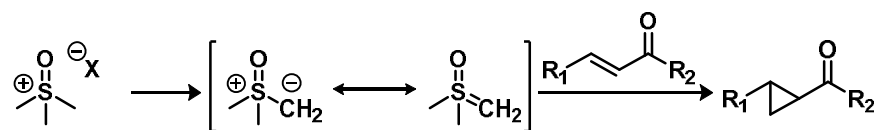


Figure 4. Catalytic copper-based asymmetric cyclopropanation a.³¹ b.³² c.³³

1.2.4 Via Michael addition and ring closure

1.2.4.1 Sulphur-based ylide

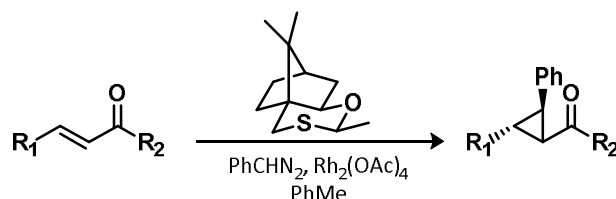
Treatment of trimethyloxosulfonium chloride or iodide (X^-) with a strong base produces the corresponding ylide which can react with a corresponding Michael acceptor. The attack on the α,β -double bond involves the transfer of the methylene of the ylide producing a cyclopropane. The aforesaid reaction was reported by Corey and Chaykovsky in 1962, demonstrating that the same reagent with a ketone produces an epoxide as major product.³⁴



Scheme 3. Sulphur based ylide cyclopropanation

Asymmetric versions of the reaction have been achieved by using diazo compounds, $Rh_2(OAc)_4$, and a camphor-derived thioacetal. In the method, the diazo compound reacts with the Rh catalyst

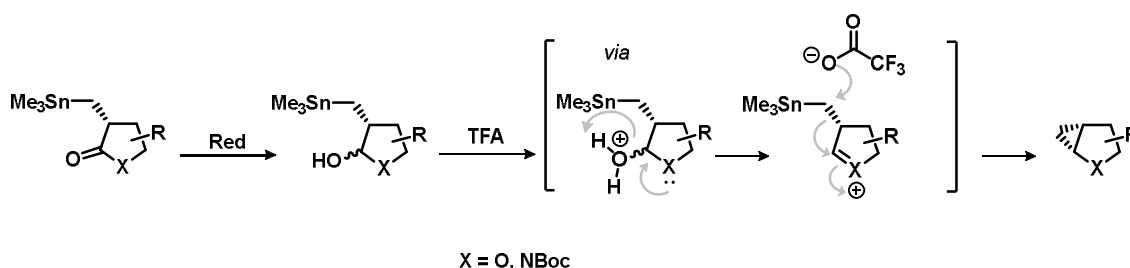
and the intermediate metal carbene transfers the alkyl chain to the chiral sulfide, forming an enantioenriched ylide which performs the cyclopropanation (Scheme 4).³⁵ Similar systems use *in-situ* generation of the diazo compound from tosylhydrazone salts.³⁶



Scheme 4. Asymmetric cyclopropanation mediated by $\text{Rh}_2(\text{OAc})_4$

1.3 Tin-mediated cyclopropanation

In 1996, Hanessian and coworkers reported the synthesis of α -methanopyrrolidines and α -methanotetrahydrofurans mediated by trimethylstannylmethyl compounds.³⁷ The cyclopropanation was triggered by the formation of an oxonium/iminium ion with further intramolecular carbocyclization.



Scheme 5. Tin-mediated cyclopropanation

The reaction allows the stereocontrolled formation of bicyclic and tricyclic methanoprolines, as well as methanopiecolic acids.^{38,39} However the synthesis of methano-tetrahydrofurans was not fully explored beyond applications of building methano-tetrahydrofurans.³⁷

1.4 Synthesis of 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofurans

For simplicity, we shall number the tetrahydrofurans as sugars. IUPAC nomenclature is used in the Experimental part (Figure 5).

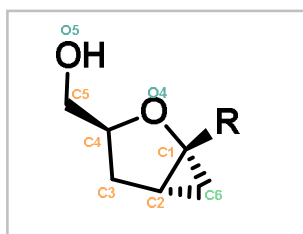


Figure 5. Numbering of the 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofuran derivatives

1-Substituted tetrahydrofurans are present in many synthetic and natural products with important biological activities, such as in antibiotics,⁴⁰ and pheromones.⁴¹ We envisaged the stereocontrolled synthesis of a new class of 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofurans using the tin-mediated cyclopropanation reported by the Hanessian group.³⁷⁻³⁹

In pursuing our objective of constraining the tetrahydrofuran ring by appending a 1,2-methano- (fused cyclopropane ring), we also speculated whether such compounds could act as biologically

active pseudo-electrophiles due to the possible formation of an incipient oxonium ion in an acidic intracellular environment (Figure 6).

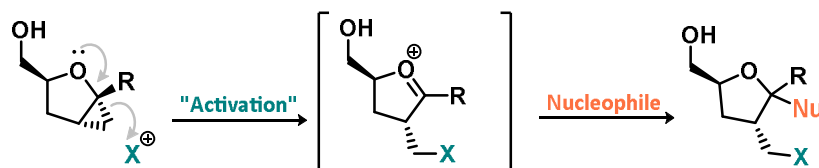
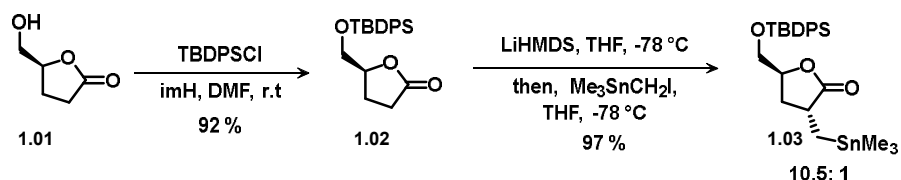


Figure 6. Hypothetical intermediate of an activated oxonium ion as a pseudo-electrophile

The synthesis of the 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofuran derivatives started with the protection of the commercially available and widely used lactone **1.01** (5g-\$80-Arkpharm) with TBDPSCl affording the compound **1.02**. The silyl protecting group was compatible for subsequent operations (Scheme 6). The protected lactone **1.02** was treated with lithium hexamethyldisilazide (LiHMDS) at -78 °C to form the required enolate.⁴² Subsequent addition of the iodomethyl trimethylstannane (Me)₃SnCH₂I⁴³ gave **1.03** in 97% yield as a 10.5:1 mixture of diastereoisomers.



Scheme 6. Synthesis of the *trans*-2-trimethylstannylmethyl lactone

The observed selectivity was attributed to the steric effect induced by the TBDPS protecting group, blocking the top face of the intermediate enolate and favoring the attack from the bottom face as shown in the Figure 7.

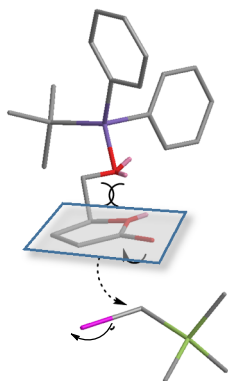
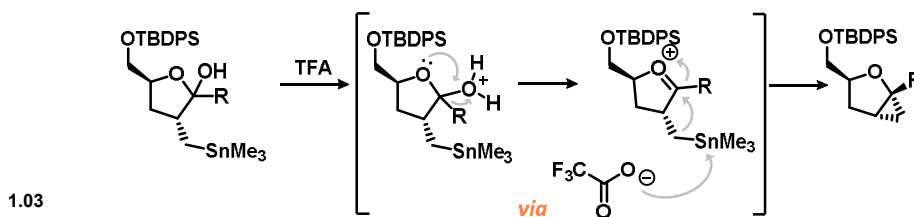


Figure 7. Selective α -alkylation

Having the desired *trans*-2-trimethylstannylmethyl lactone **1.03**, we explored the 1,2-addition of organo-lithiated nucleophiles to give the corresponding lactol intermediates in good yields. Addition of TFA at $-45\text{ }^{\circ}\text{C}$ resulted in a formation of an incipient oxonium ion which underwent cyclization with loss of the trimethylstannyl group, affording the desired 1,2-methano-1,4-substituted-tetrahydrofuran bicycles (Scheme 7).



Scheme 7. Mechanism of the intramolecular cyclization mediated by tin

Different types of organo-lithiated reagents were explored to give a variety of 1,2-methano-1,4-substituted tetrahydrofurans (Table 1). Compounds **1.04**, **1.05**, **1.07**, **1.09**, and **1.11** were prepared by deprotonation of the terminal alkynyl reagents with *n*-butyllithium and submitted to the above reaction conditions with the lactone **1.03**. To obtain **1.09** and **1.11**, the alkynyl OTBS protected reagents **1.08** and **1.10** were respectively prepared by protection of 3-buten-1-ol and 4-pentyn-1-ol with TBSCl.

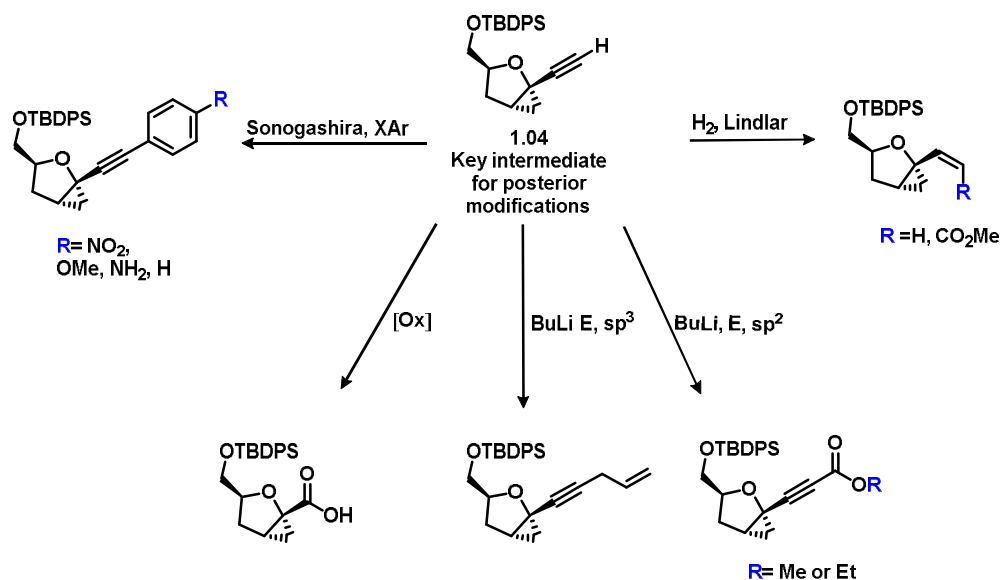
Aryllithiated compounds substituted in the *para* position with electron-withdrawing and electron-donating groups were explored. In the case of 1,2-methano-1,4-substituted-tetrahydrofuran derivatives **1.14** and **1.15**, the lithiated reagents were pre-formed by a metal-halogen exchange reaction between the 1-halide-4-substituted benzene and *n*-butyllithium in THF at -78 °C for 1 h. The preformed aryllithiated compounds were added to the lactone **1.03** to give the corresponding lactol intermediates, which by treatment with TFA afforded the *p*-fluoro and *p*-methoxy derivatives **1.14** and **1.15**, respectively.

Heterocyclic lithium reagents were also pre-formed by a metal-halogen exchange reaction with the corresponding bromo derivatives and *n*-butyllithium. Reaction with the lactone **1.03** followed by tin-mediated cyclization gave **1.12** and **1.13**.

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|--------------|------------------|------------------|--|
| | | | |
| | 1.03 | | |
| Alkynes | 1.04 49 % | 1.05 57 % | 1.07 n=1, 1.09 n=2, 1.11 n=3 39 % 42% 41% |
| Arenes | 1.06 60 % | 1.14 35 % | 1.15 40 % |
| Heterocycles | 1.12 70 % | 1.13 80 % | |

Table 1. 1,2-Addition to the lactone 1.03

Having obtained the 1,2-methano-1,4-substituted-tetrahydrofurans analogues, we envisaged further functionalization. We selected the ethynyl tetrahydrofuran derivative **1.04** as a common building block due to the variety of existing methods to diversify terminal alkynes (Scheme 8).

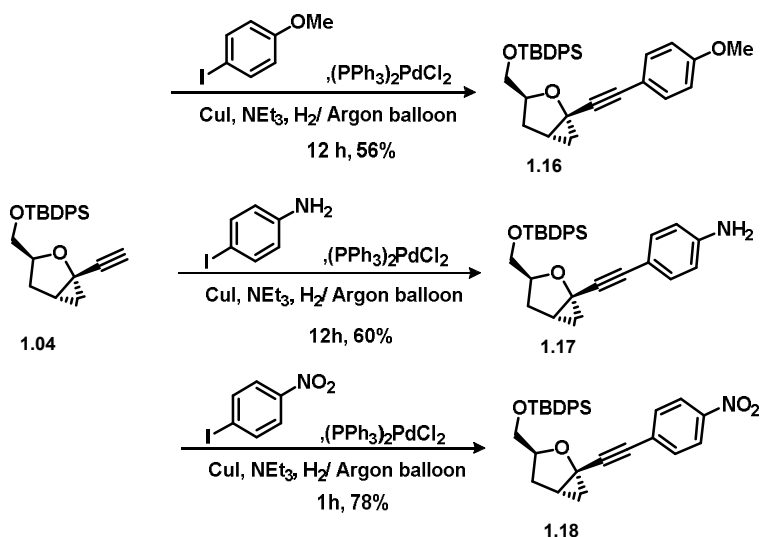


Scheme 8. Diversification of alkyne **1.04**

The Sonogashira coupling of terminal alkynes and aryl halides remains one of the most important methods for the formation of C(sp²)-C(sp) bonds.^{44,45} With the aim to diversify the alkyne **1.04** we decided to use the Sonogashira coupling to install a variety of groups.

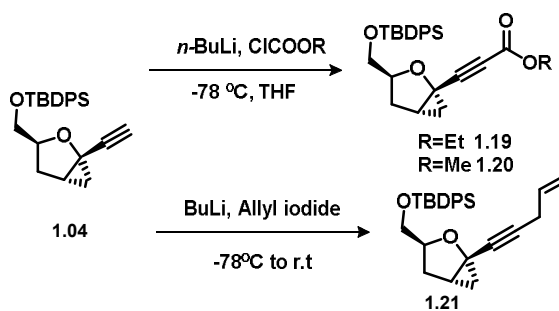
Under the Sonogashira conditions reported by Tong in 2003,⁴⁶ the coupling was performed between the alkyne **1.04** and aryl halides to study the influences of electron-withdrawing and electron-donating substituted aryl-halide partners. Using iodoaniline, 1-iodo-4-methoxybenzene and 1-iodo-4-nitrobenzene, the reactions proceeded clean and the known alkyne homocoupling Sonogashira side-products were not detected.

The coupling reaction between the alkyne **1.04**, the 4-iodoaniline and the 1-iodo-4-methoxybenzene was ~12 times slower compared with the one using 1-iodo-4-nitrobenzene **1.18**, affording **1.16** in 56% and **1.17** and 60% yield respectively. The results concurred with reported data by Plenio and Shilz in 2012,⁴⁷ in which electron-withdrawing groups were known to increase the reactivity, accelerating the reaction and improving the reaction efficiency (Scheme 9).



Scheme 9. Sonogashira cross coupling

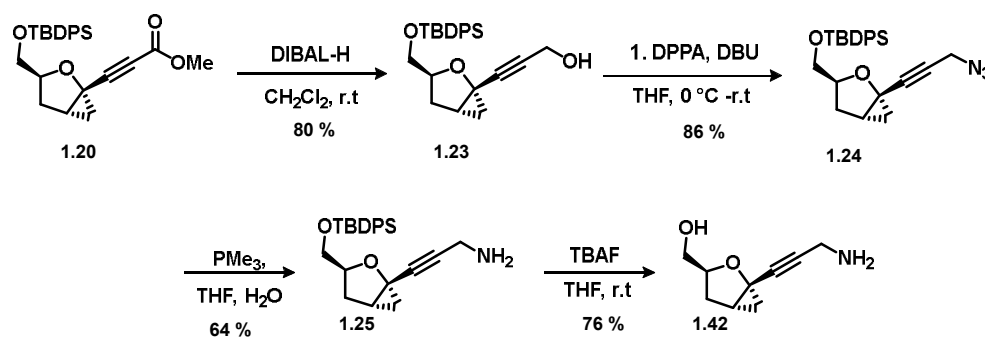
Having tested the Sonogashira cross coupling reaction, we explored other C-C bond formation by treatment of the Li acetylide with allyl iodide and chloroformate esters. Thus, the lithiated-alkyne of **1.04** was reacted with allyl iodide to give compound **1.21** which contains a chain that could be further functionalized using Grubbs metathesis,⁴⁸ Heck⁴⁹ or a hydroboration reactions⁵⁰ among others (Scheme 10).



Scheme 10. Alkyne **1.04** as nucleophile.

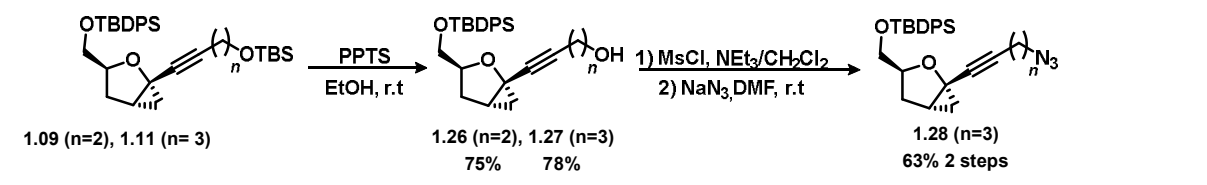
Propargyl esters **1.19** and **1.20** were obtained by reaction of the lithiated-alkyne with ethyl and methyl chloroformate respectively (Scheme 10).

Methyl ester **1.20**, was reduced using DIBAL-H to give alcohol **1.23** in good yield (Scheme 11). Subsequent treatment with DPPA gave the azide **1.24** in 86% yield. Azide **1.24** was treated with PMe_3 to form the intermediate iminophosphorane, which was then hydrolyzed to release the primary amine **1.25** in 64% yield. Treatment of sylylether **1.25** with TBAF afforded the amino alcohol **1.42** in 76% (Scheme 11).



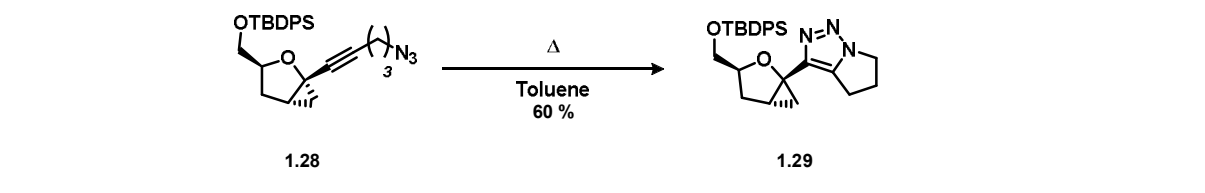
Scheme 11. Post functionalization of methyl ester **1.20**

Orthogonal deprotection of the TBS protected derivatives **1.09** (n=2) and **1.11** (n=3) with pyridinium *p*-toluenesulfonate gave respectively primary alcohols **1.26** (n=2) and **1.27** (n=3) in good yields (Scheme 12).



Scheme 12. Post-modification of the TBS compounds.

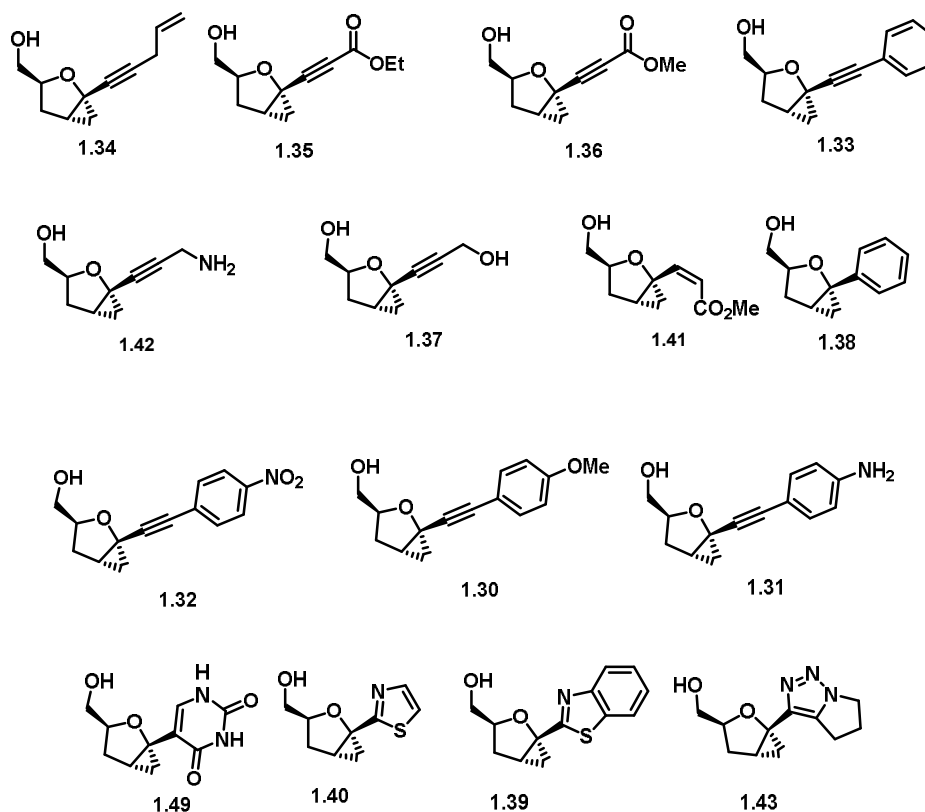
The obtained alcohol **1.27** was transformed into the mesylate and displaced with sodium azide to give the azide **1.28** in 70% yield. Azide **1.28** was subjected to a Huisgen 1,3-dipolar cycloaddition.⁵¹ Using the conditions reported by Pearson,⁵² to obtain the bicyclic triazole **1.29** in 60% (Scheme 13).



Scheme 13. Huisgen 1,3-dipolar cycloaddition

1.4.1 Deprotection of 1,2-methano-1,4-substituted-tetrahydrofuran derivatives

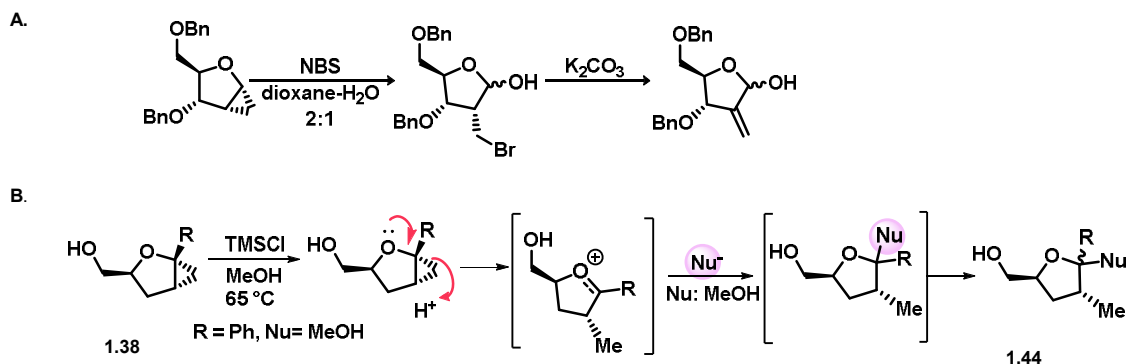
Some of the synthesized 1,2-methano-1,4-substituted tetrahydrofurans were submitted to cleavage of the TBDPS group with tetrabutylammonium fluoride, TBAF, to afford the corresponding free alcohol derivatives in good yields (Scheme 14).



Scheme 14. Deprotection of the TBDPS ethers with TBAF

Several methods of cyclopropane cleavage have been reported in 1,2-cyclopropanated pyranoid sugar derivatives. Using stoichiometric amounts of $\text{Hg}^{(\text{II})}$ salts,⁵³ strong acids,⁵⁴⁻⁵⁷ halonium ions,^{58,59} or Pt reagents.⁶⁰ To the best of our knowledge, only one example of cleavage of a

furanoid glycal has been documented using N-bromosuccinimide under solvolysis conditions (Scheme 15).⁶¹



Scheme 15. A. Cyclopropane ring opening using halonium ion reported in literature. B. Initial attempts to open the cyclopropane with TMSCl MeOH at Hanessian's group.

Stability studies of 1,2-methano-1-phenyl-4-hydromethyl-tetrahydrofuran **1.38** For example, with aqueous 0.1 N HCl in excess or with TFA in DCM, resulted in recovered of starting material. Prolonged heating of **1.38** in the presence of *p*-TsOH in refluxing toluene⁵⁷ resulted in decomposition. However, treatment of **1.38** with an excess of TMSCl in MeOH at 65°C after 24 hours afforded partial conversion to the 1-methoxy-1-phenyl-2-methyl-4-hydroxymethyl-tetrahydrofuran **1.38** (*m/z*) 223.12 (*M*+1) and 245.47 (*M*+Na) (Scheme 15.B). Further studies are in progress to evaluate the importance of electronic and other effects in the ring opening of 1,2-methano-tetrahydrofuran derivatives.

1.5 Biological data

We premised that the 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofuran derivatives might be susceptible to in vitro activation of the cyclopropane ring with assistance from the furanose oxygen via formation of an incipient oxonium ion that could be trapped by a nucleophile in biological media (Figure 8). S-Adenosyl methionine (SAM) is an universal methylating agent that mediates the transfer of methyl groups by histone methyl transferases with implications in cancer.⁶²

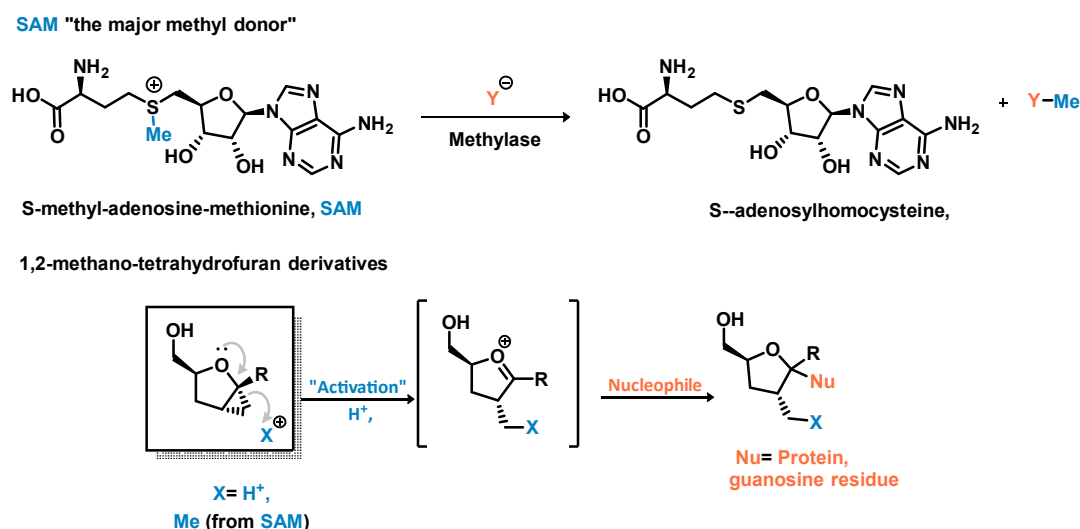


Figure 8. Hypothetical mechanism for the potential in vitro activation of the 1,2-methano-tetrahydrofuran derivatives

Thus, cyclopropanes **1.30**, **1.31**, **1.33**, **1.34**, **1.35**, **1.36**, **1.37**, **1.41** and **1.42**, were all tested as new chemical entities by the Structural Genomic Consortium, (SGC-Toronto) against a panel of 32 histone methyl transferases at 100uM and 200uM concentrations. Unfortunately, none of the compounds showed any activity.

1.6 Conclusions

- The synthesis of 1,2-methano-1-substituted-4-hydroxymethyl-tetrahydrofuran derivatives was successfully accomplished using tin-mediated cyclopropanation reported by Hanessian group.³⁷ Diverse synthetic methods to introduce different types of functionalities were used, such as aromatic rings, alkyl chains and heterocycles, among others at the C-1 position. The resulting compounds can be subjected to different types of modifications, exploiting the available functionalities.

2 Chapter 2: Synthesis of constrained nucleosides

2.1 Nucleosides in medicinal chemistry

Nucleosides and nucleotides are involved in all aspects of cellular processes such as metabolic regulation, catalysis, energy supply, and the storage of genetic information through the nucleic acids. The essential roles of nucleosides and nucleotides have inspired many studies that bridge the chemistry and biology of cellular processes.⁶³

Nucleosides are formed by the association of a heterocyclic nucleobase, a purine (adenine and guanine) or a pyrimidine base (cytosine, thymine and uracil) linked to a D-ribofuranose core, such as β -D-deoxyribofuranose or β -D-ribofuranose for DNA or RNA, respectively (Figure 9).

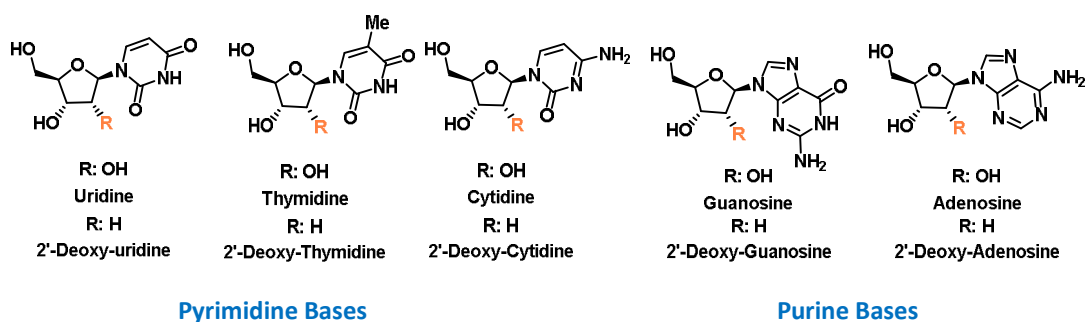


Figure 9. Natural nucleosides that constitute nucleic acids, R = H: β -D-deoxyribofuranose (DNA); R = OH β -D-deoxyribofuranose (RNA).

Nucleosides are the essential building blocks in the synthesis of nucleic acids where millions of combinations are possible using only four different nucleosides (Figure 10).⁶⁴ Deoxyribonucleic acid (DNA), is made up of four types of nucleotides, linked covalently forming a polynucleotide chain (a DNA strand) with a sugar-phosphate, thus, serving as backbone from which the bases (adenine, cytosine, guanine, and thymine) extend. A DNA molecule is composed of two single

strands bound together by hydrogen bonds between paired bases as described by the Watson - Crick Model.⁶⁵ Nucleosides can also be found as monomers, such as the cyclic adenosine monophosphate, a second messenger, that functions as a key mediator of extracellular processes in a variety of signaling pathways, including glycogen metabolism, gene regulation, and olfactory sensory transduction.⁶⁶

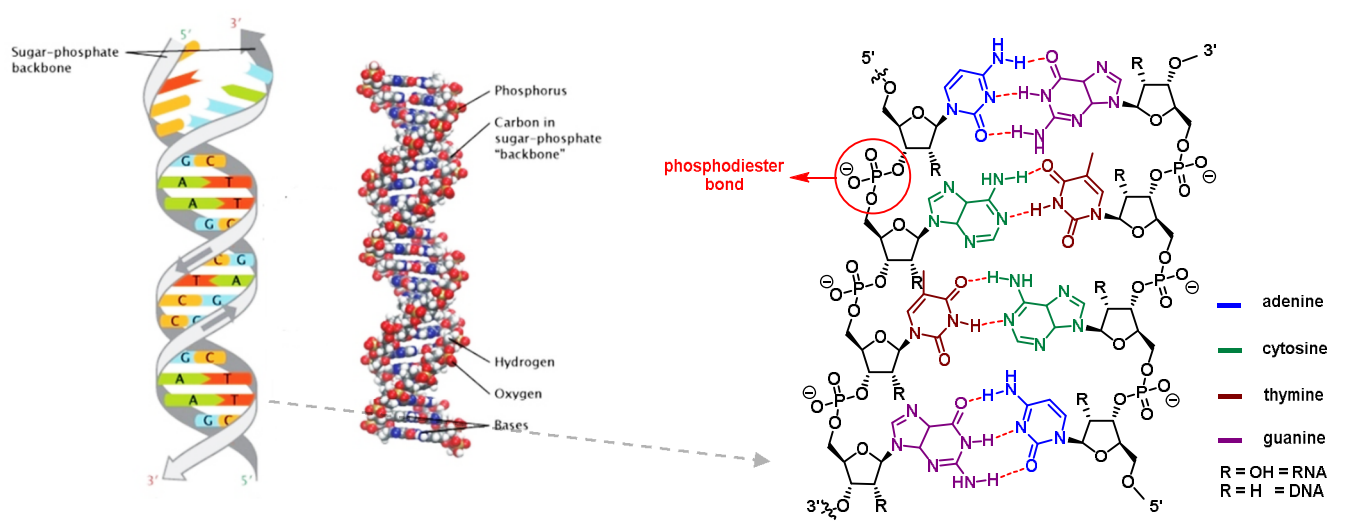


Figure 10. The double-helical structure of the DNA-nucleosides as building blocks in DNA.⁶⁷

Nucleoside and nucleotide analogues (NAs) have shown great utility as therapeutic drugs.⁶⁸ They can interact and inhibit essential enzymes such as human and viral polymerases, kinases, ribonucleotide reductase, DNA methyltransferases, purine and pyrimidine nucleoside phosphorylases (NPs) and thymidylate synthase.

Over several decades, a large number of modified nucleosides have been synthesized and evaluated for the treatment of cancer and as antiviral agents, leading to a deeper understanding of their structure-activity relationships.⁶⁸

Different strategies have been employed to modify nucleosides. In many cases, the variations have been made on the furanose moiety. Examples include: a) introduction of functionalities at different positions of the furanose ring; b) changes of the configuration at C1'; c) replacement of O4' with other atoms, such as a C-atom to form carbocyclic nucleosides; d) opening the pentose ring into an open chain structure to form acyclic nucleosides; e) fusing of pentose ring with a new ring system to form conformationally constrained nucleosides; and f) changing the pentose ring size by ring contraction or ring expansion (Figure 11).

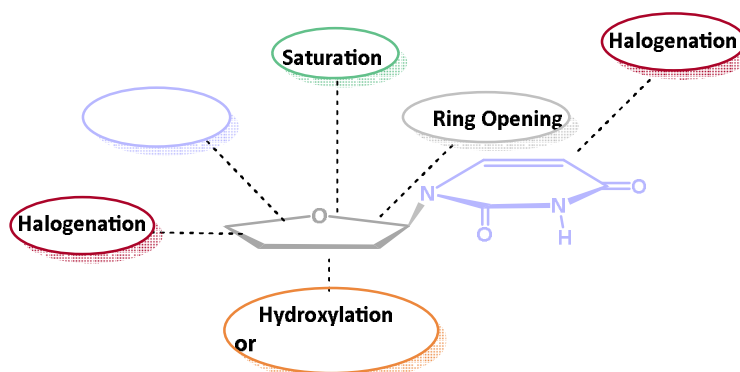


Figure 11. Chemical modifications of nucleoside furanose ring and base respectively.⁶⁸

It is interesting to highlight some of the chemically modified nucleosides with their corresponding structural modifications. Inversion of the 2'-hydroxyl group on the cytidine nucleoside leads to the nucleoside analogue Cytarabine, the first FDA nucleoside approved in

1969, for the treatment of acute myeloid leukemia (Figure 12). Exchange of the 3'-hydroxyl group of thymidine for a 3'-azide group, led to the anti-HIV agent AZT (Zidovudine), one of the older (1987) FDA approved antivirals, which has been licensed by GlaxoSmithKline (GSK).⁶⁹ Currently, there are six FDA and European Medicines Agency (EMA) approved as cytotoxic nucleoside analogues. Derivatives of 2'-deoxycytidine, deoxyadenosine and deoxyguanosine, they are used for the treatment of acute myeloid leukemia, as well as colon, kidney, stomach, breast cancer, among others indications. Approximately 25 other approved nucleoside and nucleotide analogues are used as antiviral agents for several indications; including hepatitis, HIV and herpes virus infections.⁶⁸

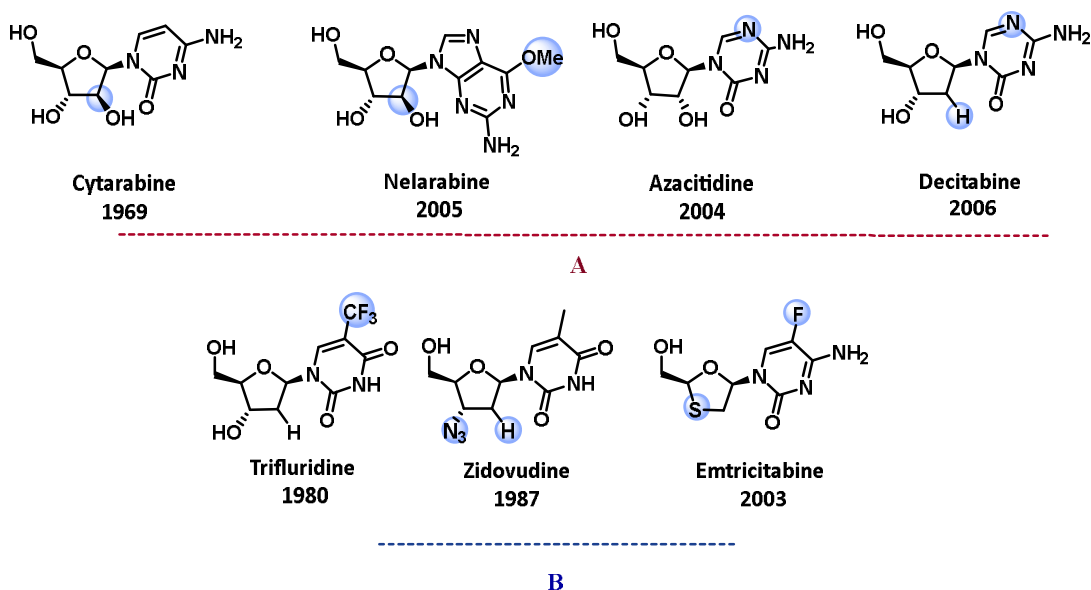


Figure 12. Examples of marketed nucleoside analogues **A)** Anticancer agents **B)** Antiviral agents

2.1.1 Mechanism of action of nucleoside analogues

Presently, therapeutic nucleoside and nucleotide analogues have been designed to mimic the physiological functions of their natural versions, with the aim to interfere with cellular metabolism and to be incorporated into DNA and RNA, resulting in inhibition of cell division and viral replication.⁷⁰ Nucleoside and nucleotide analogues enter into cells through specific nucleoside transporters.⁷¹ In order to be incorporated into the DNA strand, nucleosides must be converted to the corresponding 5'-O-triphosphates (Figure 13).

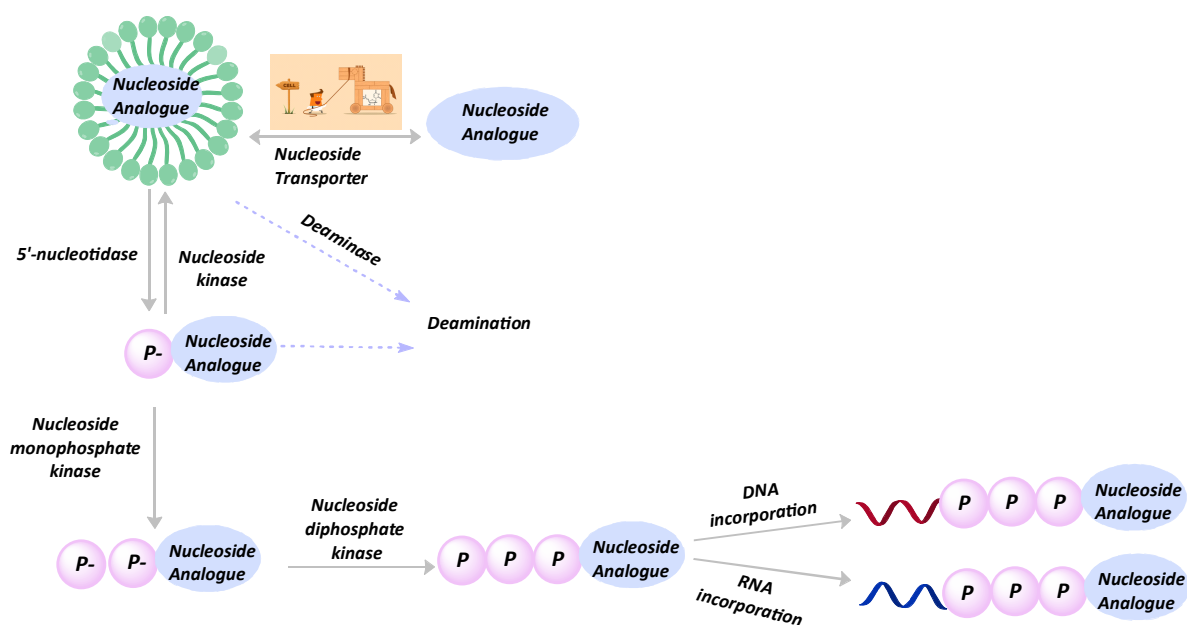


Figure 13. Mechanism of action of nucleoside analogues (Adapted from)^{72,73}

The bioactivation process depends on cellular kinases which trigger stepwise addition of phosphate groups to form the corresponding active nucleotide triphosphate.^{74,75} Formation of nucleoside 5'-O-monophosphate (MP), is the first step in the phosphorylation process (Figure

13). In general, phosphorylation is catalyzed by a nucleoside kinase encoded by the host cell or the virus infecting the host cell. Conversion of nucleoside-MPs to the corresponding 5'-O-diphosphates (DP) and triphosphates (TP) is carried out by nucleoside, nucleotidyl, and nucleoside diphosphate kinases, respectively.⁷³ Cellular kinases and virally-encoded kinases are fundamental in the metabolism and replication of cells and viruses. However, nucleotide triphosphates are not suitable as drug candidates due to their poor chemical stability, high polarity and inability to be transported across cell membranes.⁷² The first phosphorylation step has been identified as the limiting step. Several strategies allowing intracellular delivery of nucleotide analogs were developed over the past 20 years (Figure 14).⁷⁵

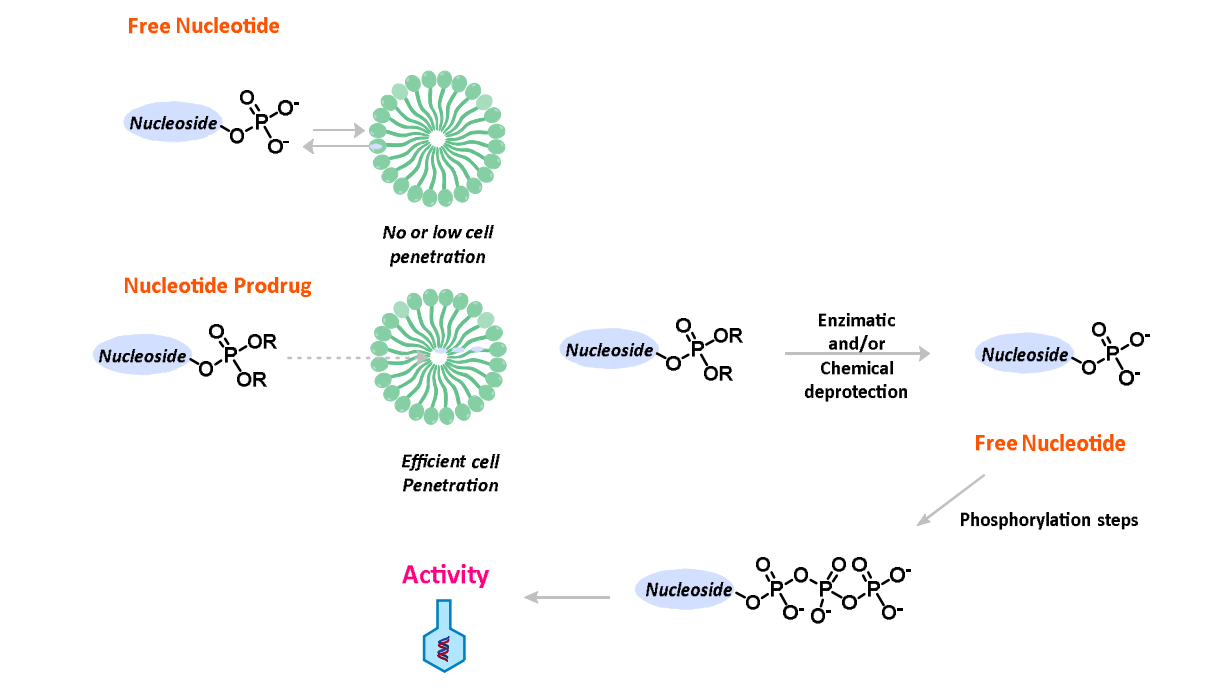
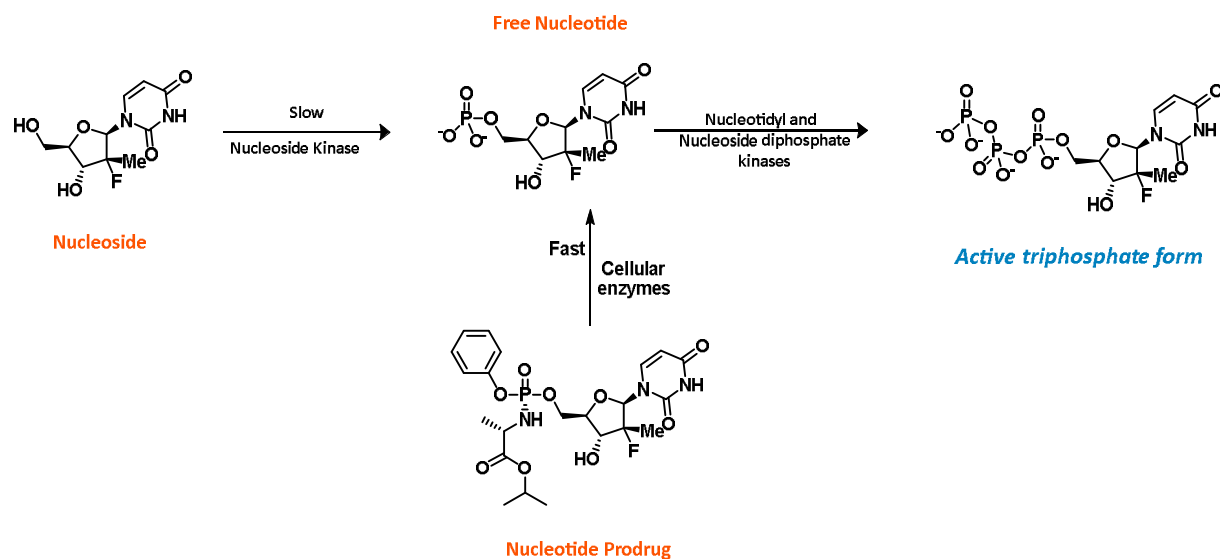


Figure 14. Mechanism of action of nucleoside monophosphate prodrugs.⁷²

In an attempt to simplify and improve the therapeutic potential of NAs, medicinal chemists have designed and prepared stable “masked” monophosphate nucleosides able to deliver the

nucleoside monophosphates intracellularly. The nucleoside monophosphate prodrugs can efficiently enter into the cells (as opposed to nucleoside monophosphates (Figure 14)). The masking groups are degraded enzymatically and/or chemically, liberating the free nucleoside analog in the monophosphate form, which can be converted intracellularly to the nucleoside triphosphate and express its biological activity (Scheme 16).

The use of phosphate prodrugs has not only proved to enhance the activity of parent nucleosides, but also, it has generated potent compounds that were previously considered not druggable due to the difficulties in the monophosphorylation step. Currently, monophosphate prodrugs have been clinically validated against the human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C virus (HCV), leading to several potent prodrugs such as Pradefovir in phase II,^{44,76} GS-7340 (TAF)⁶⁹ phase III, and the FDA-approved Tenofovir disoproxil fumarate (TDF)⁷⁷ sold under the trade name Viread, and Sofosbuvir now marketed under the trade name Sovaldi (Scheme 16).^{78,79}



Scheme 16. Example of the metabolism of Sofosbuvir prodrug

In nucleosides with antiviral activity, such as AZT,⁶⁹ the incorporation of the nucleoside or their analogues into DNA may induce the termination of chain elongation. For viruses that have a reverse transcription step, chain termination can occur during RNA-dependent or DNA-dependent DNA synthesis. Furthermore, viral polymerases often have weaker specificity for nucleotides and are therefore more suitable to incorporate them as analogues. However, the incorporation of the synthetic nucleosides is always dependent on the affinity of the polymerases for the nucleotide. After incorporation, the absence of a 3'-hydroxyl group on the furanose moiety of nucleoside and nucleotide analogues stops the formation of 3',5'-phosphodiester bonds between the analogue and the 5'-nucleoside triphosphates, which results in an early termination of the growing viral DNA or RNA chain (Figure 15).

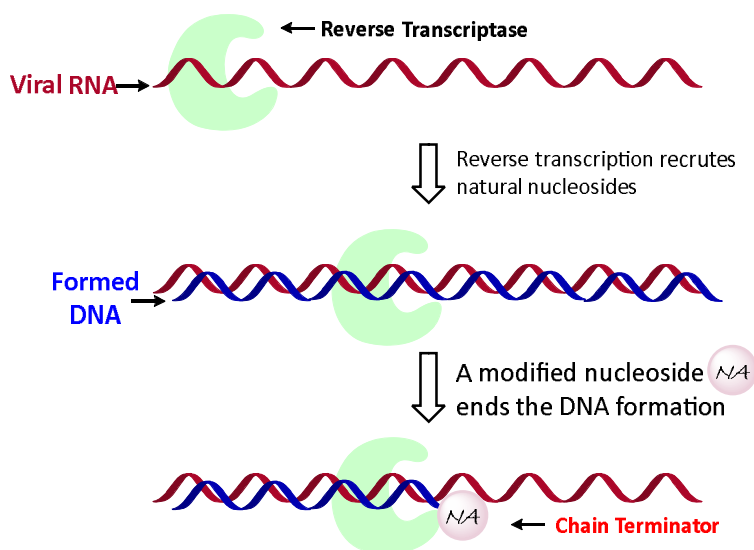


Figure 15. Mechanism of action of nucleoside reverse transcriptase inhibitors

Chain termination is observed as well with anticancer nucleosides containing the 3'-hydroxy group. They are also converted to their respective nucleotide analogues, and may inhibit the

synthesis of DNA by inhibition of DNA polymerases and/or ribonucleotide reductase.⁸⁰ The sugar conformation in the furanose core is considered a very important structural parameter in the final interaction with the target polymerases. The conformational features of natural and modified nucleosides is a broad topic of study.⁸¹

2.2 Conformation of nucleosides

The furanose conformation of natural ribo-nucleosides and deoxy-ribonucleosides is known to exist in a dynamic equilibrium between two major conformers, the North (N) and the South (S) types (Figure 16).⁸² Conformational studies of nucleosides in solution have shown that the North/South interconversion is quite fast on a NMR time scale.⁸³ When a nucleoside is part of polymeric structure such as DNA and RNA, the furanose ring is able to respond to environmental factors, such as the degree of hydration, salt concentration, metal ion coordination, protein binding, and interactions with small molecules.⁸⁴

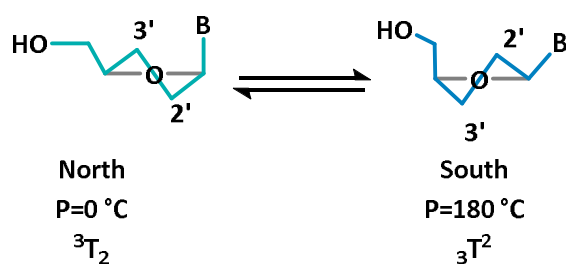


Figure 16. Dynamic two-state equilibrium of North ((N, P) 0°) and South ((S, P) 180°) nucleoside pseudorotamers in solution

Knowing the right conformation of the nucleosides and nucleotides once they are interacting with the enzymatic targets is a helpful tool for designing active compounds.

Basically, three main structural parameters determine the conformation of natural nucleosides and their analogues.

- *Syn* / *anti* orientation about the glycosyl bond (torsion angle χ): with regard to the sugar moiety, the nucleobase can adopt two principal orientations around the glycosyl C1'-nucleobase bond called *syn* and *anti* (Figure 17). *Syn* when the C-2 carbonyl of pyrimidines or N-3 of purines lies over the sugar ring, *anti* when these atoms are oriented in the opposite direction.

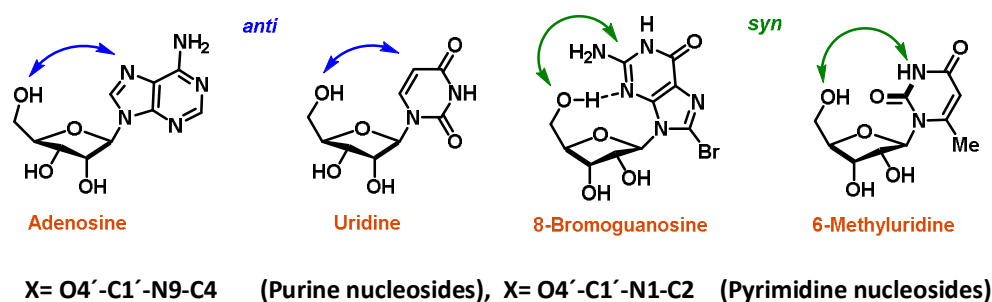


Figure 17. Disposition of the base relative to the sugar moiety

- The torsion angle γ defining the orientation of the 5'-OH with respect to C3' position and is represented by the three main rotamers γ^+ , γ^t and γ^- . The conformation of the furanose ring and its deviation from planarity are described by the pseudorotational phase angle P (0–360°) and the maximal puckering amplitude ν (0–50°). The five-membered furanose ring is generally nonplanar. It can be puckered in an envelope (E) form or in a twist (T) form, which are described by the value of P in the pseudorotation cycle (Figure 18). By convention, $P = 0^\circ$ corresponds to an absolute N conformation having a symmetrical twist form 3T_2 (C2'-*exo*-C3'-*endo*). The S conformation, 2T_3 (C2'-

endo-C3'-*exo*), corresponds to $P = 180^\circ$. Every 18° , the conformation of the furanose ring along the pseudorotation cycle alternates between envelope and twist conformations. For the typical N geometry, the conformations fluctuate between C2'-*exo* ($2E$) and C3'-*endo* (E), whereas for an antipodal S geometry, the conformations range between C3'-*exo* (E) and C2'-*endo* ($2E$). The two ranges are separated by two pseudorotational barriers that occur approximately in the Eastern (O4'-*endo*, E) and Western (O4'-*exo*, 0^0E) regions. Preference for any of these specific conformations in is determined by steric and stereoelectronic effects.⁸³

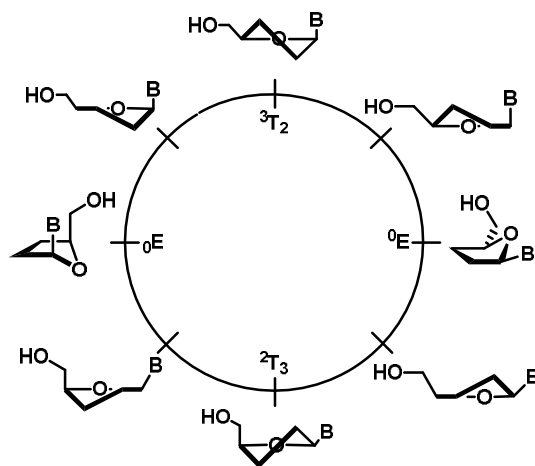


Figure 18. Pseudorotation cycle for nucleosides showing the North, South, East and West conformations. The units of P and ν_{\max} values are degrees. Envelope (E) and twist (T) forms alternate every 18° .⁸⁵

- Anomeric and gauche effects. The orientation around the C4'-C5' bond allows O5' to assume different positions relative to the furanose ring. Three principal conformations with all substituents in staggered positions are possible. These three conformations are indicated through two torsion angles (Figure 19).

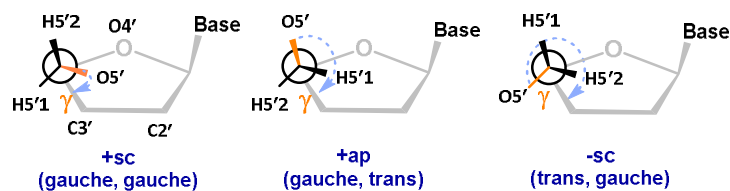


Figure 19. Orientation around the C4' and C5' bond

2.3 Synthesis of methano-constrained nucleosides

The synthesis of constrained nucleosides has become one important tool for medicinal chemistry to understand the structure activity relationship in the interaction between enzymes and nucleic acids. The incorporation of a cyclopropane into a furanose ring of a nucleoside induces some degree of constraint without affecting significantly the steric environment of a nucleoside. The strategy has been applied successfully in nucleoside chemistry to study the different effects exerted by such a modification.

In 1989, Okabe and Chu-Sun at Hoffmann - la Roche Inc. reported the synthesis of a constrained nucleoside analog, 2',3'- α -methylene-2',3'-dideoxycytidine via a homologous Ferrier reaction (Figure 20). The compound showed a weak anti HIV activity.⁸⁶ Later on, Kawana and Kuzuhara in 1992, reported the synthesis of 4',5'-fused cyclopropane containing nucleosides by 1,2-hydride shift rearrangements and β -elimination reactions of sulfonylated ribonucleosides,⁸⁷ unfortunately, no biological data was reported. In 2006, Math   et al, reported the synthesis of a variety of 3',4'-methano-arabino-nucleoside derivatives with different functional groups at the C-2' position, such as *exo*-methylene and azido groups. They also studied the conformation of

the thymine nucleosides by molecular modeling, establishing that the analogues were locked into the south-east hemisphere of the pseudorotated cycle (between a 0T_1 and a 2E conformation).

A new class of locked nucleosides, restricted by a difluoromethylene bridge between the C3'-C4' bond was reported in 2007 by Robins *et al.*⁸⁸ Their synthesis involved the addition a difluorocarbene (carbenoid) to vinyl ethers within 3',4'-unsaturated nucleosides derived from adenosine and uridine (Figure 20). The authors claimed that the electron-withdrawing effects of two fluorine atoms β to the furanosyl ring oxygen (O4') would be expected to confer stability under conditions that result in chemical or enzymatic cleavage of naturally occurring nucleosides.

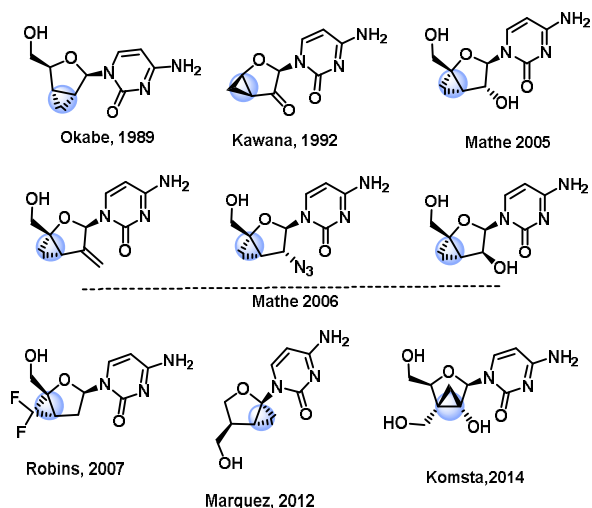


Figure 20. Selected locked nucleoside analogues.

Marquez has studied various conformationally rigid bicycle *C*-nucleoside,⁸⁹ to determine the North/South conformational preferences of a number of nucleoside(tide) and binding enzymes for their natural substrates.⁸⁴ The drop in the affinity of some enzymes with these substrates was attributed to the loss of electronic interactions, such as hydrogen bonding with key amino acids

at the active site or stereo electronic interactions with the base through the anomeric effect, due to the missing oxygen on the cycle (Figure 21).⁹⁰

Adenosine Deaminase Activity (established by kinetic parameters)

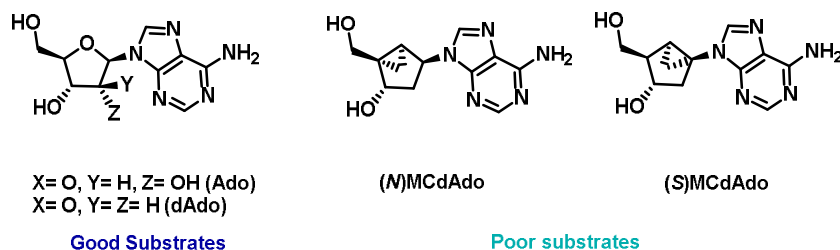


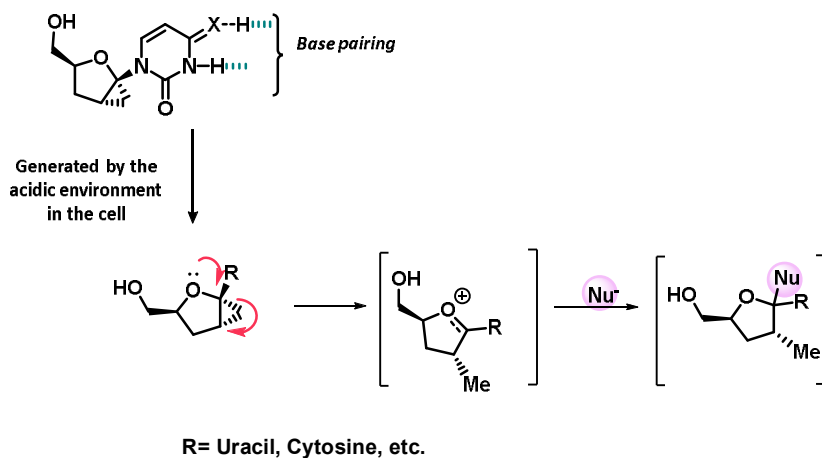
Figure 21. Comparison of adenosine deaminase activity.⁹⁰

In 2012, Ludek and Marquez, reported the synthesis of a new series of conformationally north-locked pyrimidine nucleosides.⁹¹ The nucleosides analogues consisted of an oxabicyclo hexane scaffold with the purpose of mimicking in a closer way the tetrahydrofuran ring of the natural nucleosides. The anti-HIV activity of the uridine, thymidine, and cytidine analogues was studied in human osteosarcoma (HOS) cells. Only the cytidine analogue showed moderate activity in HOS-313 cells.⁹¹

2.3.1 Synthesis of 1',2'-methano-2',3'-dideoxynucleosides

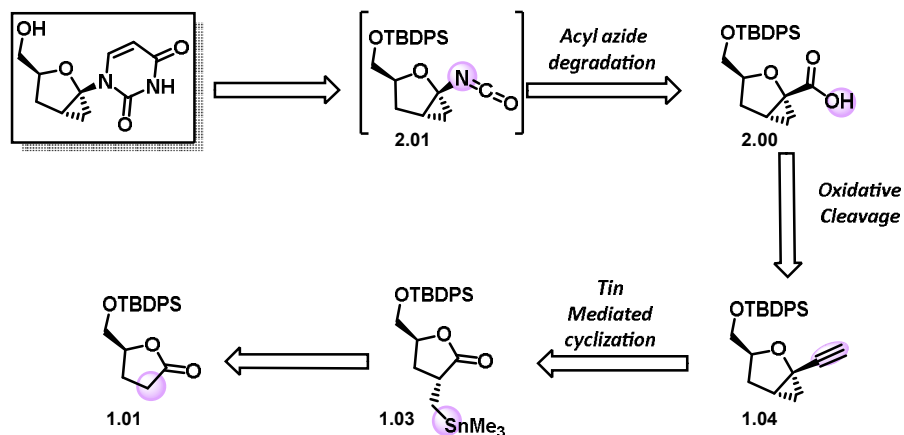
As a prototypical models of a methano-constrained nucleoside, we envisaged the synthesis of 1',2'-methano-2',3'-dideoxyuridine, and 1',2'-methano-2',3'-dideoxycytidine and their 5'-phosphoramidates to examen their potential antiviral activity compared to Sofosbuvir.⁷⁸

A hypothetical proposal relied on the possibility of base pairing with other nucleosides especially in a cellular environment. We also speculated whether the acidic environment of the cell would activate the cyclopropane ring via protonation and attack by a nucleophile such as guanidine residue (Scheme 17).



Scheme 17. Hypothetical cleavage of the cyclopropane

2.3.2 Synthesis strategy



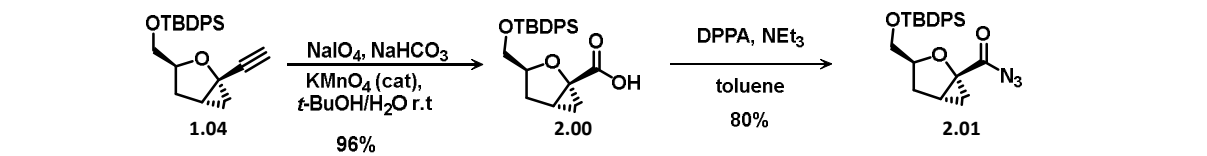
Scheme 18. Retrosynthetic analysis of 1',2'-methano-2',3'-dideoxyuridine

We envisaged that the uracil nucleobase moiety could be built from an intermediate isocyanate which could be obtained through a Curtius rearrangement of an acyl azide glycosyl functionality, and by trapped the *in-situ* by a nucleophile. The approach has been successfully applied to introduce the nucleobase moiety in various pyrimidine-nucleosides analogues.^{91,92} The acyl azide **2.01** may be prepared from the carboxylic acid **2.0**, which may be easily accessible by oxidative cleavage of the alkyne derivative **1.04** (Scheme 18).

2.3.4.1 Synthesis of 1',2'-methano-2',3'-dideoxyuridine

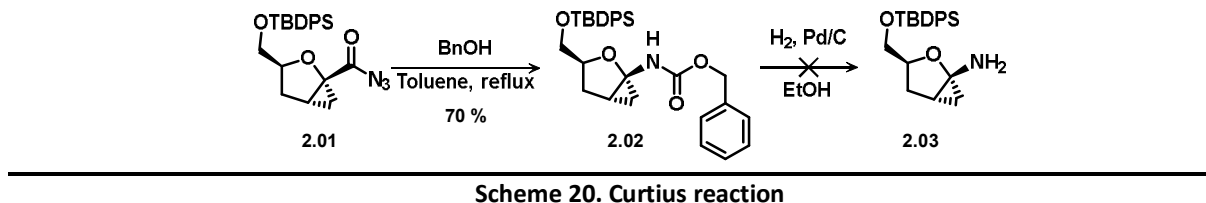
Starting from the readily available alkyne **1.04**, oxidative cleavage of the triple bond afforded carboxylic acid **2.00** in high yield. In the next step, the carboxylate was transformed into acyl

azide **2.01** with diphenyl phosphoryl azide, DPPA, and the latter was isolated in 80% yield as a colorless oil (Scheme 19).



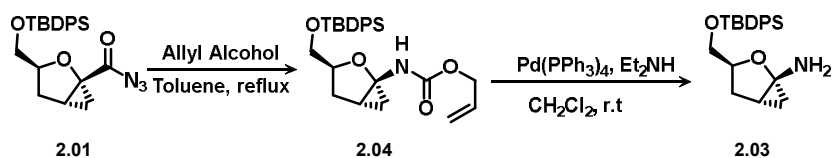
Scheme 19. Synthesis of the acyl azide key intermediate

The acyl azide **2.01** was subjected to a thermal Curtius rearrangement using benzyl alcohol to trap the isocyanate intermediate, leading to protected benzyloxy carbamate **2.02**. However, cleavage of the Cbz group **2.02** by hydrogenolysis, to obtain the free amine was not successful, and led to decomposition as evidenced by TLC (Scheme 20).



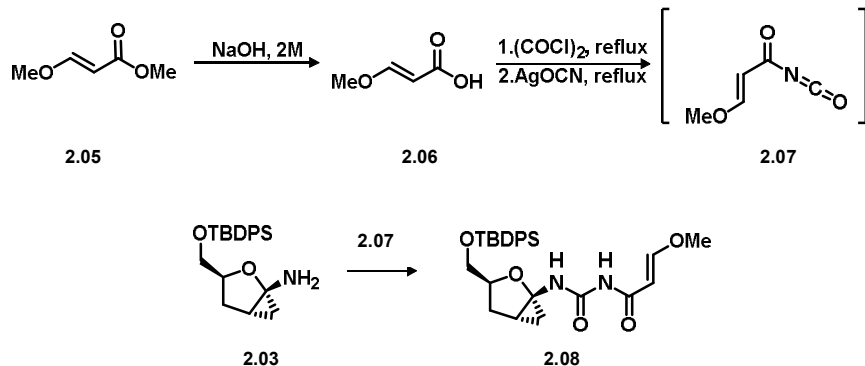
Scheme 20. Curtius reaction

Using allyl alcohol as nucleophile instead of benzyl alcohol in the Curtius step, the corresponding N-alloc carbamate **2.04** was afforded and submitted to cleavage with palladium-tetrakis(triphenylphosphine), Pd(PPh₃)₄ to give the desired amine **2.05** in quantitative yield (Scheme 21).⁹³



Scheme 21. Deprotection step of the N-alloc derivative

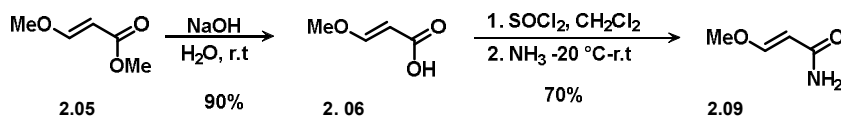
With the primary amine **2.03** in hand, the plan was to form the urea intermediate **2.08**, by reaction with β -methoxyacryloylisocyanate **2.07** (prepared as shown in Scheme 22). Unfortunately, after several attempts, the desired compound was obtained in low yield and poor reproducibility, we attributed to the highly moisture sensitive character of the AgOCN required for the reaction (Scheme 22).



Scheme 22. Synthesis of 1',2'-methano-acrylurea intermediate through the β -methoxyacryloylisocyanate

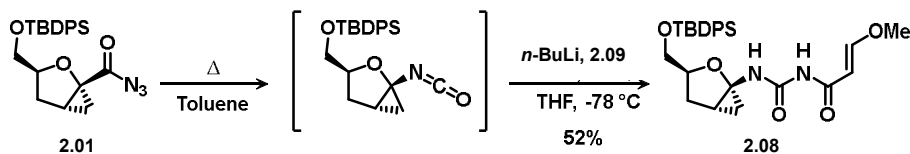
In 1992, Jung and Trifunovich reported an efficient synthesis of 2',3'-dideoxynucleosides by trapping the generated isocyanate from the Curtius rearrangement with the lithium salt of (*E*)-3-methoxyacrylamide.⁹⁴ The synthesis of (*E*)-3-methoxyacrylamide **2.09** started from the (*E*)-

3-methoxyacrylic acid **2.06**, which was converted to the acyl chloride with SOCl_2 , and reacted subsequently with ammonia to give the acrylamide **2.09** in good yields (Scheme 23).



Scheme 23. Synthesis of (*E*)-3-methoxyacrylamide

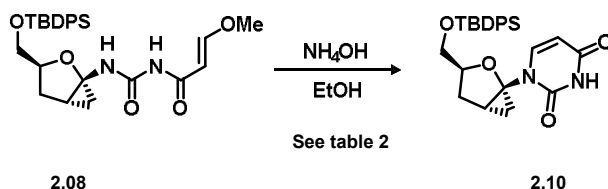
(*E*)-3-Methoxyacrylamide **2.09** was treated with *n*-BuLi to form the lithium salt which was reacted with the intermediate isocyanate formed in the Curtius reaction to afford urea compound **2.08** in 52% yield (Scheme 24).



Scheme 24. Synthesis of 1',2'-methano-acrylurea intermediate

The next challenge was to find conditions for the cyclization step to form the uracil base. Reported methods have used strong acid mediated cyclization (H_2SO_4),⁹² or cyclization mediated by bases such as NH_4OH . Initial attempts using basic conditions $\text{NH}_4\text{OH}/\text{EtOH}$ at 100 °C (in a sealed tube for 5h as reported by Marquez)⁹¹ afforded the desired uracil base. However, the reaction time was relatively long and some degradation of the compound was observed in the course of the reaction. Thus, we decided to use microwave conditions (Table 2). After

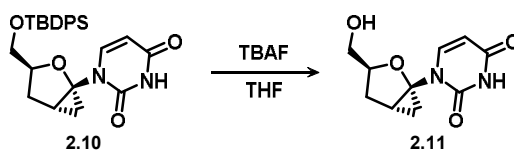
several attempts, it was found that the best results were obtained when the reaction was done at 160 °C for 6 min affording the desired uracil in 72 % yield.



| Exp # | Method | Conditions | Time | T (°C) | Scale | yield |
|-------|-------------|-------------------------|--------|--------|--------|---|
| 1 | Sealed tube | NH ₄ OH/EtOH | 5 h | 100 °C | 100 mg | 42% |
| 2 | Sealed tube | NH ₄ OH/EtOH | 5 h | 100 °C | 20 mg | 52% |
| 3 | Sealed tube | NH ₄ OH/EtOH | 10 min | 160 °C | 5 mg | TLC-co-spot with the desired product and ¹ H-crude NMR were done |
| 4 | Microwave | NH ₄ OH/EtOH | 6 min | 160 °C | 20 mg | 72% |
| 5 | Microwave | NH ₄ OH/EtOH | 6 min | 160 °C | 100 mg | 69% |

Table 2. Microwave assisted cyclization.

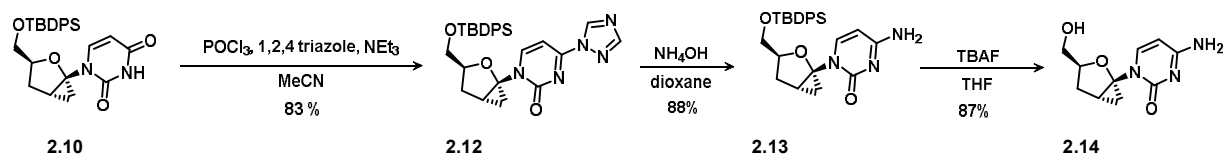
Finally, the protected nucleoside **2.10** was treated with tetrabutyl ammonium fluoride, to give the 1',2'-methano-2',3'-dideoxyuridine **2.11** in 84% yield (Scheme 25).



Scheme 25. Deprotection step

2.3.4.2 Synthesis of 1',2'-methano-2',3'-dideoxycytidine

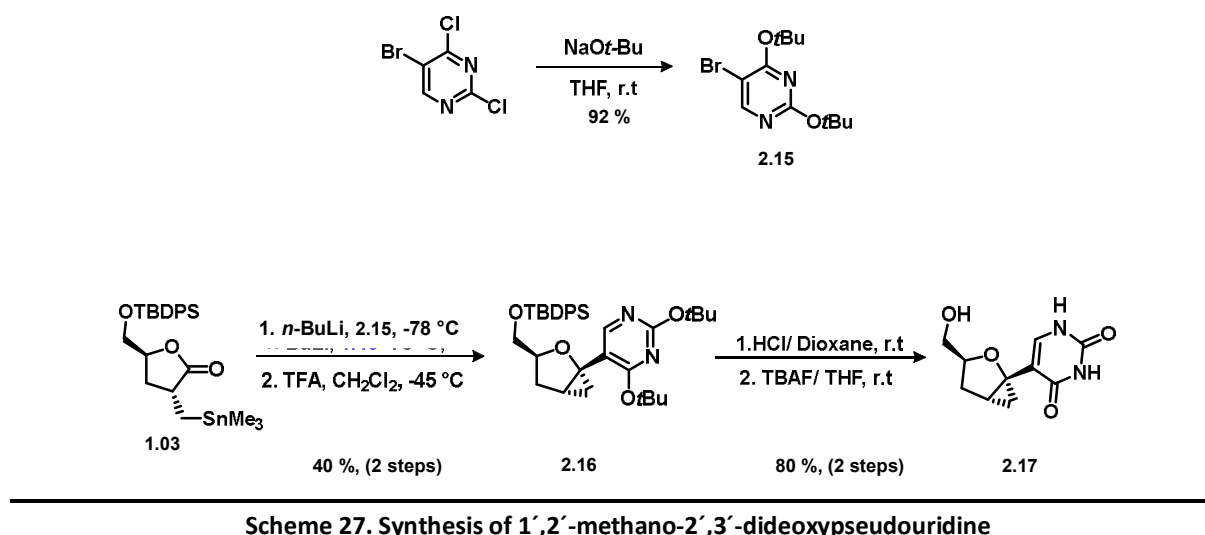
Essentially, a known procedure to obtain the cytidine analogue from the advanced uridine base moiety was used.⁹⁵ Treatment of **2.10** with 1,2,4-triazole afforded compound **2.12** which was submitted to ammonolysis, leading to the desired cytosine base **2.13**. Cleavage of the TBDPS protecting group with TBAF afforded the desired constrained cytidine analogue **2.14** in good yield (Scheme 26).



Scheme 26. Synthesis of the 1',2'-methano-2',3'-dideoxycytidine

2.3.4.3 Synthesis of a 1',2'-methano-2',3'-dideoxypseudouridine

A short synthesis of a 1',2'-methano-2',3'-dideoxypseudouridine analogue was envisaged using the tin-mediated cyclopropanation. Starting from the lactone **1.03** and treatment with the lithiated 1,3-pyrimidine (prepared according to the reported procedure),^{96,97} followed by cyclization triggered by TFA afforded adduct **2.16**. Cleavage of the OtBu ethers under acidic conditions and subsequent deprotection of the TBDPS group with TBAF afforded the 1',2'-methano-2',3'-dideoxypseudouridine **2.17** in 80 % over two steps (Scheme 27).



2.4 Crystallographic and conformational analysis

In order to study the solid-state conformation of the synthesized nucleoside analogues 1',2'-methano-2',3'-dideoxyuridine **2.11** and 1',2'-methano-2',3'-dideoxycytidine **2.14**, we obtained X-ray quality crystals. The crystal structures obtained for both analogues corroborated all the assigned structures and stereochemistry.

2.4.1. Conformation of 1',2'-methano-2',3'-dideoxyuridine

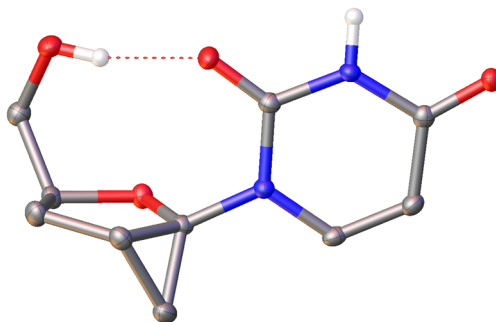


Figure 22. X-ray crystal structure of 1',2'-methano-2',3'-dideoxyuridine

The conformation of nucleoside analogues has been studied using NMR experiments, molecular modeling and crystallographic data,^{82,90,98} We analyzed the conformation of the 1',2'-methano-2',3'-dideoxyuridine based on the obtained crystallographic data.

The pseudorotational phase angle P ($0-360^\circ$) and the maximal puckering amplitude ν_{\max} ($0-50^\circ$) were calculated for **2.11** $P = 0^\circ$ corresponds to an absolute N conformation having a symmetrical twist form 3T_2 ($C2'-exo-C3'-endo$), while the S antipode twist, 2T_3 ($C2'-endo-C3'-exo$), corresponds to $P = 180^\circ$.⁸² Based on the X-ray structure of the nucleoside **2.11** it was determined that the furanose ring is restricted to a 3T_2 North, $C2'-exo-C3'-endo$ conformation ($P = 0.8225^\circ$, $\nu_{\max} = 5.8806^\circ$) with a relatively short puckering amplitude of 5.8806. Thus, the presence of the cyclopropane ring between the C1' and C2' locks and flattens the furanose ring.

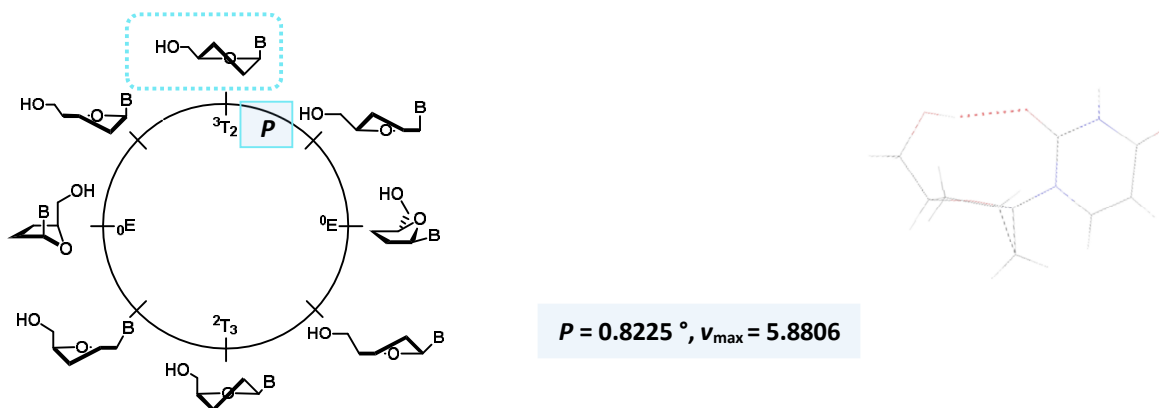


Figure 23. Pseudorotational cycle for nucleosides; determination of the phase angle of compound **2.11**

The calculated torsion angle χ for bicycle **2.11** (O4'-C1'-N1-C2) was 67° . As evidenced in the crystal structure (Figure 24), the nucleobase points towards to the sugar moiety in a *syn* orientation, furthermore an intramolecular hydrogen bond is formed between the pyrimidinone carbonyl oxygen and the 5'-OH, favoring the *syn* orientation.

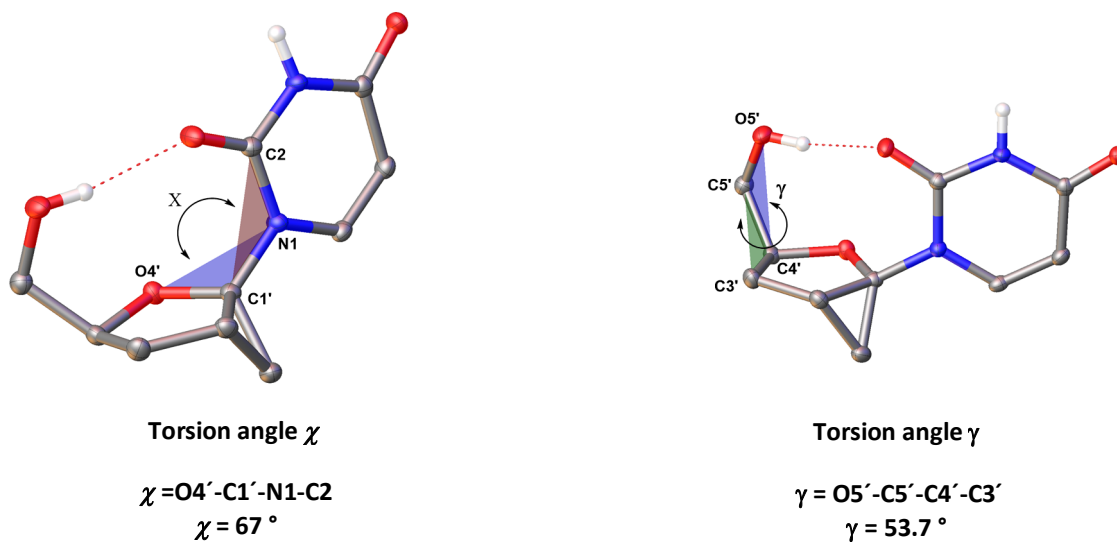


Figure 24. Torsion angles χ and γ

The torsion angle γ calculated for bicycle **2.11** was 53.7° ($\gamma = \phi_{\text{oc}} = \text{O5}'\text{-C5}'\text{-C4}'\text{-C3}'$) defining thus the orientation of the 5'-OH with respect to C3' of the furanose ring. As observed in the X-

ray structure, the hydrogen bond formed between the O2 and the proton of the 5'-OH favored the observed orientation between C4'-C5' (Figure 24).

2.4.2. Conformation of 1',2'-methano-2',3'-dideoxycytidine

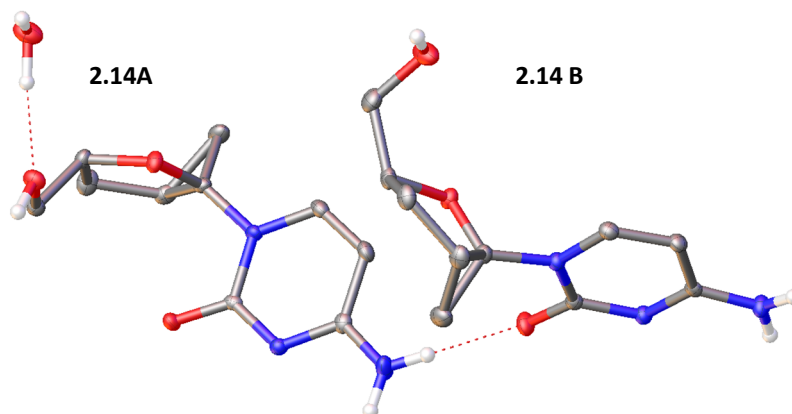


Figure 25. X-ray crystal structure of 1',2'-methano-2',3'-dideoxycytidine

The conformation analysis of the 1',2'-methano-2',3'-dideoxycytidine **2.14** was based on the X-ray crystal structure. Interestingly **2.14** showed two different conformations. (For the purpose of the study they were designed as **2.14A** and **2.14B**) (Figure 25).

The pseudorotational phase angle P and the maximal puckering amplitude ν_{\max} calculated for compound **2.14A** and **2.14 B** were restricted to a 3T_2 North, C2'-exo-C3'-endo conformation ($P = 0.8875^\circ$ and -0.3806° ; $\nu_{\max} = 16.6301^\circ$ and 3.6441° , for **2.14A** and **2.14B** respectively). The major difference between the two conformations was observed in the puckering amplitude, probably influenced by the hydrogen bond formed between O2 of **2.14B** and one of the protons of N5 of **2.14A**, which makes a small change on the conformation of the furanose. The flattening

effect on the furanose ring conferred by the cyclopropane moiety to **2.11** was also evidenced in **2.14** (in both conformations observed **A** and **B**.)

Torsion angle χ

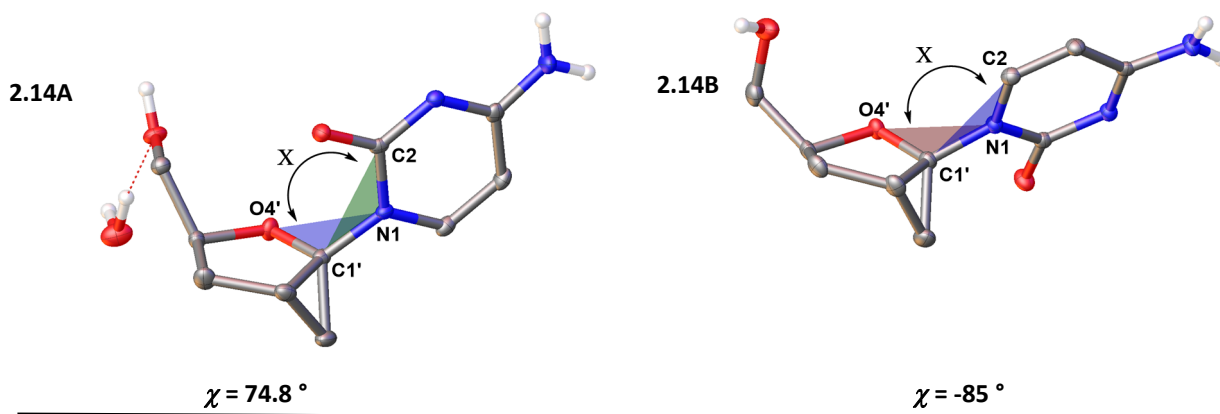
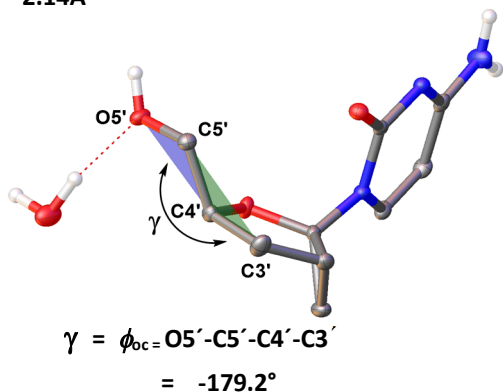


Figure 26. Orientation of the nucleobase for 2.14A and 2.14B

The calculated torsion angle χ for compound **2.14** (O4'-C1'-N1'-C2') was 74.8° for **2.14A** (Figure 26). The nucleobase was in *syn* disposition toward to the furanose. Interestingly in the second conformation observed for **2.14B** (Figure 26, B), the oxygen O2 of the carbonyl forms an intermolecular hydrogen bond with one of the hydrogens of the amine group in the cytosine base of **2.14A**, changing the disposition of its nucleobase towards C1' compared to **2.14A**. The torsion angle χ calculated for **2.14B** was -85.0° and the nucleobase was in *anti*-disposition.

Torsion angle γ

2.14A



2.14B

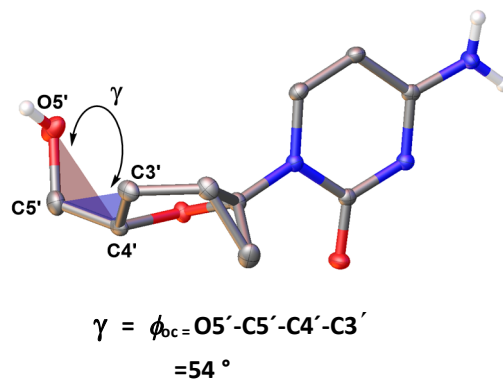
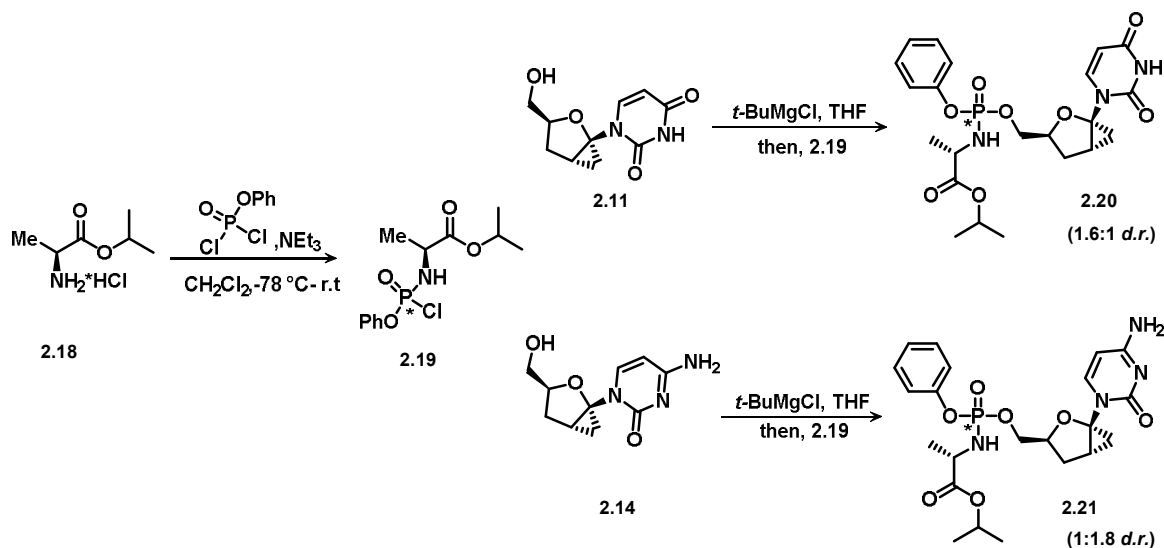


Figure 27. Torsion angle γ of compound 2.14

The torsion angles γ were calculated respectively for conformers **2.14A** and **2.14B** ($\gamma = \phi_{oc} = \text{O5}'\text{-C5}'\text{-C4}'\text{-C3}'$) at -179.2° and 54° (Figure 27). The previous results and the fact that the cytidine analogue **2.14** crystallized in two different conformations indicate that the torsion angles of the nucleoside can be more affected by environment than the geometry of the furanose.⁸⁴

2.5 Synthesis of phosphoramidate prodrugs

Finally, in order to test the 1',2'-methano-nucleosides analogues synthesized as potential antiviral agents, preparation of their phosphoramidate derivative was required. Applying the reported conditions by McGuigan to form the aryloxyphosphoramidates,⁷⁵ alcohols **2.11** and **2.14** were converted into the corresponding aryloxyphosphoramidate-prodrugs. The synthesis started with the preparation of the phosphochloridate intermediate **2.19** by treatment of isopropyl *L*-alaninate hydrochloride with phenyl dichlorophosphate and triethylamine, the reagent was stable up to two weeks stored at -18 °C. After treatment of the 1',2'-methano-nucleosides **2.11** and **2.14** with *tert*-butyl magnesium chloride. The respective alcoxides were treated with phosphorochloridate **2.19** affording the 5'-phosphoramidate-uridine **2.20** as a mixture of diastereoisomers (³¹P NMR: δ 2.83, 2.70; 1.6:1 *d.r.*) and the 5'-phosphoramidate-cytidine **2.21** as a mixture of diastereoisomer (³¹P NMR: δ 3.65, 3.56; 1:1.8 *d.r.*) (Scheme 28).



Scheme 28. Synthesis of phosphoramidate prodrugs **2.20** and **2.21**

2.6 Biological data

1',2'-methano-nucleosides **2.11**, **2.14**, and phosphoramidates **2.20** , **2.21** (mixture of diastereoisomers) were tested as potential antivirals using cell-based assays for viral replication across the herpes virus family, CMV, VZV, HSV1, HSV2 and EBV courtesy of Merck laboratories Rahway, NY. These compounds were also tested as inhibitors for infection of CALU-1 cells with GFP labeled RSV. A cell-based assay was also use to test for inhibition of HIV. Unfortunately, none of the compounds showed activity in the assays.

2.7 Conclusions

Starting from cheap and commercially available (*S*)-4-hydroxymethyl-butyrolactone, stereocontrolled syntheses of three constrained nucleosides analogues, 1',2'-methano-2',3'-dideoxypseudouridine, **2.17** (*C*-nucleoside); 1',2'-methano-2',3'-dideoxyuridine, **2.11** and 1',2'-methano-2',3'-dideoxycytidine, **2.14** were achieved, by way of the key intermediate, **1.04** via the tin cyclopropanation strategy.

X-ray analysis was used to characterize the structures of 1',2'-methano-2',3'-dideoxynucleosides **2.11** and **2.14** and to study the solid state conformation of these nucleosides. Both analogues were shown to be locked into a north type (N) conformation.

Applying the reported conditions by McGuigan, the aryloxyphosphoramidate-prodrugs, **2.20** and **2.21** were successfully synthesized.

Compounds **2.11**, **2.14**, **2.20** and **2.21** did not show any antiviral activity against in bioassays for HIV, RSV and the herpes family.

3.0 Experimental Section

3.1 General experimental details

All non-aqueous reactions were run in oven (120 °C) or flame-dried glassware under a positive pressure of argon, with exclusion of moisture from reagents and glassware, using standard techniques for manipulating air-sensitive compounds, unless otherwise stated. Anhydrous tetrahydrofuran, diethyl ether, toluene, and dichloromethane were obtained by passing these solvents through activated columns of alumina, while all other solvents were used as received from chemical suppliers. Reagents were purchased and used without further purification. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous material, unless otherwise stated.

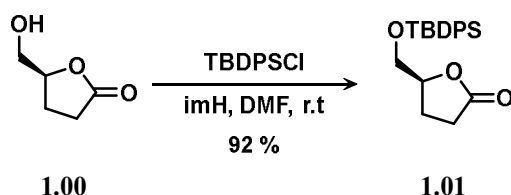
Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica plates (SIL 60, G-25, UV254) that were visualized using a UV lamp (254 nm) and developed with an aqueous solution of ceric ammonium molybdate, or an ethanolic solution of *p*-anisaldehyde.

Flash chromatography¹⁰¹ was performed using SiliaFlash® P60 40-63 μm (230-400 mesh) silica gel. Note that when the solvents ratios are described, they refer to volumetric ratios. NMR spectra were recorded on Bruker AV-300, ARX-400, AV-400 or AV-500 instruments, calibrated using residual undeuterated solvent as an internal reference (CHCl_3 , $\delta = 7.26$ ppm), and reported in parts per million relative to tetramethylsilane (TMS $\delta = 0.00$ ppm) as follows: chemical shift (multiplicity, coupling constant (Hz), integration). The following abbreviations

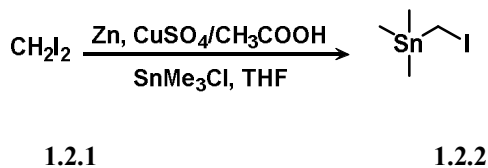
were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets. High resolution mass spectra (HRMS) were recorded at the Centre Régional de Spectrométrie de Masse de l'Université de Montréal on an Agilent LC-MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments.

3.2 Experimental data chapter 1.

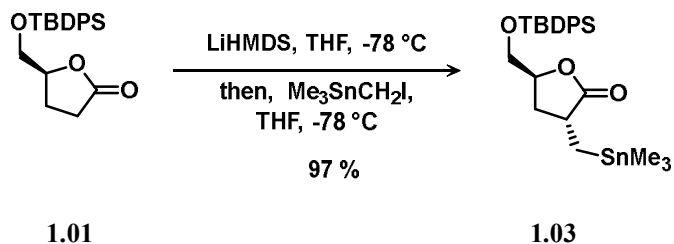
3.2.1 Synthesis of 1,2-methano-1,4-hydroxymethyl-tetrahydrofuran derivatives



(S)-5-(((*tert*-Butyldiphenylsilyl)oxy)methyl)dihydrofuran-2(3H)-one (1.01). To a solution of the lactone⁹⁹ **1.00** (5.00g, 43.06mmol) in DMF (48 mL), was added imidazole (6.45 g, 94.73 mmol) in one portion at r.t., followed by slow addition of *tert*-butyldiphenylsilyl chloride (13.02 g, 12.32 mL, 47.37 mmol). The reaction mixture was stirred for 1 hour at room temperature. Then, the DMF was removed under reduced pressure. The residue was partitioned between CHCl₃ and water. The layers were separated and the organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with hexanes containing 0-10% of EtOAc to yield **1.01** as a white solid (Rf: 0.29 hexanes, 14 g, 39.62 mmol, 92%). ¹H NMR (300 MHz, CDCl₃) δ 7.71 – 7.62 (m, 4H), 7.49 – 7.36 (m, 6H), 4.67 – 4.55 (m, 1H), 3.88 (dd, J = 11.3, 3.3 Hz, 1H), 3.69 (dd, J = 11.3, 3.4 Hz, 1H), 2.68 (ddd, J = 17.4, 10.1, 7.2 Hz, 1H), 2.51 (ddd, J = 17.6, 9.6, 6.8 Hz, 1H), 2.37 – 2.15 (m, 2H), 1.06 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 177.44, 135.64, 135.53, 129.91, 127.83, 79.96, 65.46, 28.55, 26.73, 23.64, 19.19. HRMS (ESI⁺) *m/z* calcd for: C₂₁H₂₇O₃Si: (M+H) 355.1724 found 355.17291; C₂₁H₃₀NO₃Si: (M+NH₄⁺) 372.1990 found 372.1994.

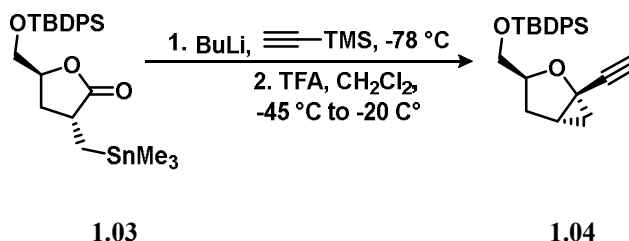


(Iodomethyl) trimethylstannane (1.2.2). To a mixture of granular zinc (13.20 g, 201.90 mmol) and CuSO₄ (0.32 g, 2.02 mmol) glacial acetic acid (10 mL) was added and the resulting heterogeneous mixture was stirred and heated at 60 °C for 5 min. The volatiles were removed and acetic acid (10 mL) was added to the remaining solid which was re-submitted to same previous conditions. The mixture was filtered and the remaining zinc-copper solid was washed with diethyl ether (3 x 25 mL), and dried under *vacuum* for 15 min. To the dried solid (Zn-Cu) in THF (30 mL) a solution of CH₂I₂ (53.80 g, 198.86 mmol, 16.5 mL) in THF (50 mL) was added at r.t dropwise via cannula, the mixture was stirred for 4 h. The reaction mixture was cooled to 0 °C, filtered under Ar and transferred via cannula to a flask. The resulting filtrate was treated dropwise with a solution of trimethyltin chloride (1.0 M in THF, 21.20 g, 106.39 mL, 106.39 mmol) and stirred at r.t. for 3h. The reaction mixture was diluted with hexanes and quenched with 1.0 M hydrochloric acid. The organic layer was collected, washed with more 1.0 M hydrochloric acid. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel flash chromatography eluting with hexanes to yield **1.22** (Rf: 0.65 hexanes, 23.10 g, 71 %) as a colorless liquid. ¹H and ¹³C NMR data matched with previously reported data.⁴³



(3*R*,5*S*)-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)3((trimethylstannyl)methyl)dihydrofu-

ran-2(3*H*)-one) (1.03). To a solution of lactone **1.01** (20.0 g, 56.41 mmol) in anhydrous THF (564 mL) a solution of LiHMDS (1M in THF, 62.06 mL, 62.06 mmol) was added dropwise at -78°C (Internal temperature) over a period of one hour using a syringe pump. After 2h, Me₃SnCH₂I **1.2.2** (20.63 g, 67.70 mmol) in THF (17 mL) was added dropwise via cannula. The reaction was kept at -78°C overnight and quenched with a saturated aqueous solution of NH₄Cl (40 mL) at -78 °C. The reaction mixture was allowed to warm to r.t., the organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to yield **1.03** as a mixture of stereoisomers 10.5:1 *trans/cis* (as ascertained by ¹H NMR (300 MHz, CDCl₃) δ 4.52 (dq, *J* = 8.8, 2.9 Hz) and 4.43 (dt, *J* = 10.1, 4.2 Hz); 3.86 (dd, *J* = 11.4, 3.0 Hz) and 3.74 (dd, *J* = 11.4, 4.5 Hz).). The residue was purified by silica gel flash chromatography eluting with hexane containing EtOAc (2%) to yield **1.03** (Rf: 0.38 EtOAc 5% in hexanes, 29.08 g, 97 %) as a mixture of diastereoisomers colourless oil which by the time become an oily white solid. Major Diastereoisomer: ¹H NMR (300 MHz, CDCl₃) δ 7.75 – 7.60 (m, 4H), 7.47 – 7.38 (m, 6H), 4.52 (dq, *J* = 8.8, 2.9 Hz, 1H), 3.86 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.65 (dd, *J* = 11.3, 3.0 Hz, 1H), 3.07 – 2.91 (m, 1H), 2.48 (ddd, *J* = 12.2, 9.4, 2.6 Hz, 1H), 1.95 (dt, *J* = 12.7, 9.2 Hz, 1H), 1.26 – 1.14 (m, 1H), 1.05 (s, *J* = 4.6 Hz, 9H), 1.02 – 0.96 (m, 1H), 0.18 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 181.27, 135.78, 135.65, 133.05, 132.55, 130.05, 127.99, 65.83, 37.88, 34.47, 26.89, 19.28, 14.13. HRMS (ESI⁺) *m/z* calcd for C₂₅H₄₀O₃Si [120Sn]N 550.1794 (M+NH₄)⁺ found 550.1805.

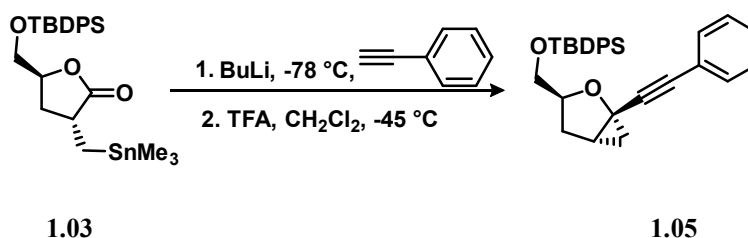


***tert*-butyl(((1*R*,3*S*,5*S*)-1-ethynyl-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)diphenylsilane**

(1.03). To a 2 neck round flask containing a solution of ethynyltrimethylsilane (7.12 g, 10.31 mL, 72.46 mmol) in anhydrous THF (362 mL) at -60 °C, a solution of *n*-BuLi (2.5 M in hexanes, 28.98 mL, 72.46 mmol) was added dropwise over a period of 30 minutes using a syringe pump. After 40 minutes, the mixture was cooled to -78 °C and transferred dropwise via cannula to a 3 neck round bottom flask containing a solution of **1.03** (11.00 g, 20.70 mmol) in anhydrous THF (207 mL) at -78 °C. The reaction mixture was stirred for 2 hours at -78 °C and allowed to warm slowly to -45 °C, stirred for 1h. Quenched with pH 7 buffer solution (20 mL). The cold reaction mixture was diluted with EtOAc. The layers were separated. The aqueous phase was extracted with EtOAc (2 x 200 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

To the resulting crude lactol in CH₂Cl₂ (1.0 L) at -45 °C, trifluoroacetic acid (1.61 g, 1.10 mL, 14.10 mmol) was added dropwise (resulting in a dark orange solution). The internal temperature was maintained below -20 °C. After 20 minutes. The reaction was quenched with saturated aqueous solution of NaHCO₃, stirred for 10 minutes at r.t. The layers were separated. The aqueous layer was extracted with CH₂Cl₂ (1 x 50 mL). The combined organic layers was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by

silica gel flash chromatography eluting with hexanes containing EtOAc (0-3%) to yield alkyne **1.04** as colorless oil (Rf: 0.6 hexanes/ EtOAc (2%), 3.82 g, 49 % over two steps) ^1H NMR (400 MHz, CDCl_3) δ 7.71 (td, J = 7.8, 1.6 Hz, 4H), 7.47 – 7.35 (m, 6H), 3.95 – 3.86 (m, 1H), 3.77 (dd, J = 10.6, 4.5 Hz, 1H), 3.69 (dd, J = 10.6, 5.4 Hz, 1H), 2.50 (s, 1H), 2.20 – 2.10 (m, 1H), 2.05 (dd, J = 12.3, 7.1 Hz, 1H), 1.88 – 1.81 (m, 1H), 1.18 (t, J = 5.9 Hz, 1H), 1.08 (s, 9H), 1.01 (dd, J = 8.9, 6.4 Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 135.74, 135.66, 133.60, 133.48, 129.68, 127.68, 82.46, 80.13, 72.09, 65.36, 57.91, 31.67, 26.88, 24.92, 19.72, 19.30. HRMS (ESI $^+$) m/z calcd for: $\text{C}_{24}\text{H}_{28}\text{O}_2\text{SiNa}$: ($\text{M}+\text{Na}$) $^+$ 399.1751 found 399.1750.



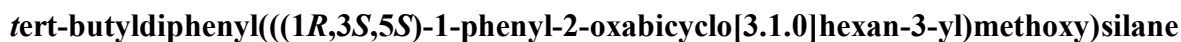
***tert*-butyldiphenyl(((1*R*,3*S*,5*S*)-1-(phenylethynyl)-2-oxabicyclo[3.1.0]hexan-3-**

yl)methoxy)silane (1.05). To a solution of ethynylbenzene (109.00 mg, 1.07 mmol, 0.12 mL) in THF (5.0 mL) at -78 °C, a solution of *n*-BuLi (2.5 M, 1.12 mmol, 0.45 mL) was added dropwise over a period of 10 min, after completion of the addition, the reaction was stirred for 1h, then was transferred dropwise via cannula to a flask containing a solution of lactone **1.03** (189.00 mg, 0.356 mmol) in THF (2.0 mL) at -78 °C. The reaction was allowed to warm to -45 °C over a period of 1.5 hours, stirred for 1h. The reaction was quenched by addition of pH 7 buffer solution. The cold reaction mixture was diluted with EtOAc (60 mL). The layers were

separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

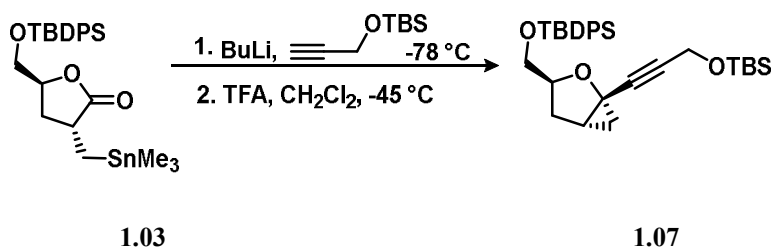
The resulting crude lactol was dissolved in CH₂Cl₂ (18 mL) cooled at -45 °C, trifluoroacetic acid (101.00 mg, 0.89 mmol, 0.07 mL) was added dropwise, resulting in an orange solution. The reaction internal temperature was keep it at -45 °C. The reaction was stirred at the same temperature until consumption of the starting material. After 30 min saturated solution of NaHCO₃ was added. The layers were separated. The aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-2%) to yield **1.05** (Rf: 0.6 hexanes 10% EtOAc, 92.03 mg 57% over two steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.77-7.71 (m, 4H), 7.46 – 7.37 (m, 8H), 7.33 – 7.29 (m, 3H), 3.97 (m, 1H), 3.82 (dd, J = 4.4, J = 10.6 Hz, 1H), 3.75 (dd, J = 10.5, 5.3 Hz, 1H), 2.12 (ddd, J = 0.64 Hz, J = 7.1 Hz J = 12.2 Hz, 1H) 1.94 (dt, J = 5.3, J = 9.1 Hz, 1H), 1.30 (t, 1H, J = 5.8), 1.15 (m 1H), 1.11 (s, 9H) ¹³C NMR (100 MHz, CDCl₃) δ 135.70, 135.60, 133.60, 133.40, 131.60, 129.60, 128.10, 128.00, 127.60, 122.90, 87.80, 83.70, 79.90, 65.40, 58.40, 31.70, 26.80, 25.20, 20.0, 19.3.

HRMS (ESI⁻) *m/z* calcd for C₃₀H₃₁O₂Si (M-H): 451.2083 found 451.2093.



The resulting lactol was dissolved in CH₂Cl₂ (10 mL) cooled to -45 °C, trifluoroacetic acid (62.50 mg, 0.55 mmol, 0.05 mL) was added dropwise, resulting in an orange solution, keeping internal temperature at -45 °C. The reaction was quenched by addition of saturated solution of NaHCO₃. The layers were separated. The aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-2%) to yield **1.06** (Rf: 0.6 hexanes 10% EtOAc, 54.10 mg, 60% over two steps) as a colourless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.76 – 7.71 (m, 4H), 7.46 – 7.30 (m, 10H), 7.28 – 7.20 (m, 1H), 4.18 – 4.09 (m, 1H), 3.80 (qd, J = 10.6, 4.8 Hz, 2H), 2.18 (dd, J = 7.8, 3.0 Hz, 2H), 1.76 (qd, J = 5.7, 3.1 Hz, 1H), 1.38 – 1.34 (m, 1H), 1.19 (dd, J = 9.0, 6.4 Hz,

1H), 1.08 (s, 9H). ¹³C NMR (126 MHz, CDCl₃) δ 141.20, 135.80, 133.76, 129.75, 128.20, 127.79, 126.36, 124.80, 79.72, 69.79, 65.79, 32.21, 26.96, 25.56, 19.41, 18.90. HRMS (ESI⁺) *m/z* calcd for C₂₈H₃₂NaO₂Si (M+Na) 451.2064 found 451.2074

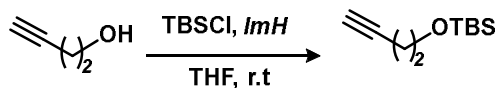


***tert*-butyl(((1*R*,3*S*,5*S*)-1-(3-(((*tert*-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-2-**

oxabicyclo[3.1.0]hexan-3-yl)methoxy)diphenylsilane (1.07). To a solution of *tert*-butyldimethyl (2-propynyloxy) silane (128.22 mg, 0.75 mmol, 0.15 mL) in THF (1.9 mL) at -78 °C, *n*-BuLi (2.5 M, 0.77 mmol, 49.43 mg, 0.30 mL) was added dropwise over a period of 10 min, after completion of addition, the reaction was stirred for 1h, transferred dropwise via cannula to a flask containing a solution of the TBDPS protected lactone **1.03** (100.00 mg, 0.19 mmol) in THF (1.90 mL) at -78 °C for 1 h, warmed slowly to -45 °C and stirred for 1 hour. Quenched with pH 7 buffer solution (20 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

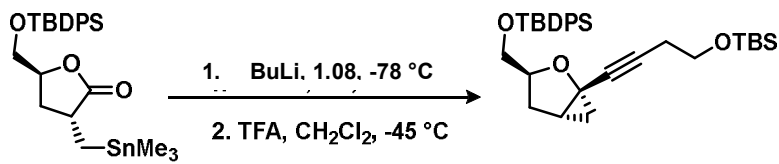
The resulting lactol was dissolved in CH₂Cl₂ (9.50 mL) and cooled to -45 °C. Trifluoroacetic acid (64.38 mg, 0.043 mL, 0.564 mmol) was added dropwise. The internal temperature of the reaction was maintained below -20 °C. After 20 minutes saturated aqueous NaHCO₃ was added, the reaction mixture was stirred for 10 minutes. The layers were separated. The aqueous layer

was extracted with dichloromethane (2 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-3%) to yield **1.07** (Rf: 0.5 hexanes 2% EtOAc, 38 mg, 39 % over two steps) as a colourless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.68 (ddd, J = 7.5, 4.3, 1.8 Hz, 4H), 7.45 – 7.33 (m, 6H), 4.35 (s, 2H), 3.87 (dt, J = 12.6, 6.7 Hz, 1H), 3.74 (dd, J = 10.5, 4.5 Hz, 1H), 3.65 (dd, J = 10.5, 5.6 Hz, 1H), 2.17 – 1.99 (m, 2H), 1.83 – 1.73 (m, 1H), 1.15 (t, J = 5.8 Hz, 1H), 1.05 (s, 9H), 0.96 (dd, J = 8.8, 6.5 Hz, 1H), 0.91 – 0.87 (m, 9H), 0.12 – 0.07 (m, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 135.84, 135.77, 133.73, 129.77, 127.79, 79.97, 65.52, 58.19, 52.07, 31.93, 29.85, 26.98, 25.99, 24.80, 19.76, 19.41, 18.44, -4.94. HRMS (ESI⁺) *m/z* calcd for C₃₁H₄₅O₃Si₂ (M+H)⁺ 521.2902, found 521.2903.



1.08

(But-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (1.08). As reported by Ley¹⁰⁰ to a solution of but-3-yn-1-ol (500.00 mg, 6.92 mmol, 0.53 mL) and imidazole (1.18 g, 17.30 mmol) in THF (12 mL) at r.t. *tert*-butylchlorodimethylsilane (1.25 g, 8.30 mmol) was added. After stirring at room temperature for 3 h, the reaction mixture was filtered through a silica pad and concentrated under reduced pressure to yield **1.08** (Rf 0.7 EtOAc/ Hexanes 2:8). ¹H NMR (400 MHz, CDCl₃) δ 3.35 (t, J = 7.1 Hz, 2H), 2.02 – 1.95 (m, 2H), 1.56 (t, J = 2.7 Hz, 1H), 0.57 – 0.51 (m, 9H), - 0.27 – -0.33 (m, 6H) ¹³C NMR (75 MHz, CDCl₃) δ 81.27, 69.46, 61.74, 25.86, 22.85, 18.26, - 5.35.



1.03

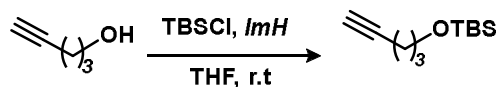
1.09

***tert*-butyl(((1*R*,3*S*,5*S*)-1-(4-((*tert*-butyldimethylsilyl)oxy)but-1-yn-1-yl)-2-**

oxabicyclo[3.1.0]hexan-3-yl)methoxy)diphenylsilane (1.09). To a solution of the but-3-yn-1-yloxy)(*tert*-butyl)dimethylsilane (170.70 mg 0.93 mmol) in THF (3.09 mL)) at -78 °C, *n*-BuLi (59.31 mg 2.50 M, 0. 37 mL) was added dropwise over a period of 10 min, after completion of addition, the reaction was stirred for 1h, then, transferred dropwise via cannula to a flask

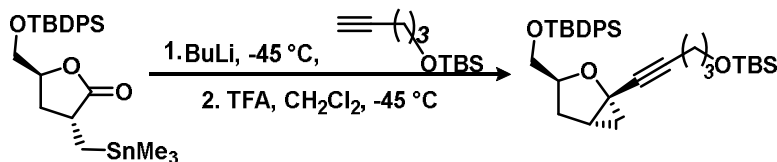
containing a solution of **1.03** (164.00 mg, 0.31 mmol), THF (3.09 mL) at -78 °C for 1 h and let it warm slowly to -45 °C, maintained at this temperature for 1 hour followed by addition of pH 7 buffer solution (15 mL). The organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure.

To the Crude lactol in CH₂Cl₂ (15.40 mL) at -45 °C, trifluoroacetic acid (0.07 mL, 0.52 mg, 0.92 mmol) was added dropwise. The internal temperature of the reaction was maintained below -20 °C and the reaction progress was monitored by TLC. After 20 minutes, saturated aqueous solution of NaHCO₃ was added, the reaction mixture was stirred for 10 minutes. The aqueous phase was extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-3%) to yield **1.09** (Rf: 0.5 hexanes EtOAc (2%), 66 mg 42 % over two steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.72 – 7.63 (m, 4H), 7.48 – 7.33 (m, 6H), 3.85 (dt, J = 12.7, 6.7 Hz, 1H), 3.78 – 3.62 (m, 4H), 2.44 (t, J = 7.4 Hz, 2H), 2.13 – 2.04 (m, 2H), 1.77 – 1.66 (m, 1H), 1.26 (t, J = 7.1 Hz, 1H), 1.12 (t, J = 5.8 Hz, 1H), 1.06 (s, 9H), 0.89 (d, J = 6.0 Hz, 9H), 0.06 – -0.79 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 135.83, 135.75, 133.75, 133.65, 129.75, 127.77, 127.76, 81.51, 79.70, 79.61, 65.73, 62.05, 58.44, 32.13, 26.98, 26.03, 24.51, 23.49, 19.40, 19.30, 18.46, -5.14. HRMS (ESI⁺) *m/z* calcd for C₃₂H₄₇O₃Si₂ (M+H)⁺ 535.3058 found 535.3055.



1.10

***Tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (1.10).** Protection procedure followed as reported by Ley.¹⁰⁰ To a solution of 4-pentyn-1-ol (500.00 mg, 5.77 mmol, 0.55 mL) and imidazole (981.00 mg, 14.41 mmol) in THF (10 mL) was added *tert*-butylchlorodimethylsilane (1004.00 mg, 6.92 mmol) at r.t. After stirring at room temperature for 3 h, the reaction mixture was filtered through a pad of silica and concentrated under reduced pressure, to yield alkyne **1.10** (Rf: 0.7 hexanes/EtOAc 1:9). ¹H NMR (400 MHz, CDCl₃) δ 3.81 (t, J = 6.0 Hz, 2H), 2.45 (s, 1H), 2.37 (td, J = 7.0, 2.6 Hz, 2H), 1.87 – 1.77 (m, 2H), 1.03 (s, 9H), 0.18 (s, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 83.95, 68.43, 61.34, 31.62, 25.96, 18.32, 14.85, -5.36. Spectra consistent with known data.



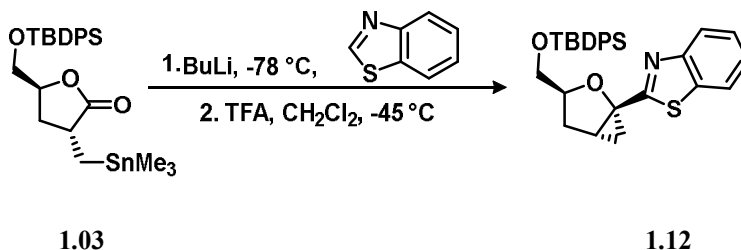
1.03

1.11

***Tert*-butyl(((1*R*,3*S*,5*S*)-1-(5-(((*tert*-butyldimethylsilyl)oxy)pent-1-yn-1-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)diphenylsilane (1.11)** To a solution of *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane (145.01 mg 0.73 mmol) in THF (3.18 mL) a solution of *n*-BuLi (45.21 mg 2.50 M 0.28 mL) was added dropwise over a period of 10 min, after completion of addition, stirred for 1h. Transferred dropwise via cannula to a flask containing a solution of **1.03** (125.00 mg, 0.24 mmol) in THF (2.3 mL) at -78 °C for 1 h and warmed slowly

to -45 °C and stirred for one hour. The reaction was quenched with a pH 7 buffer solution. The cold reaction mixture was diluted with EtOAc, the layers were separated. The aqueous layer was extracted with EtOAc (2 x 40 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

To the resulting crude lactol in CH₂Cl₂ (11.8 mL) at -45 °C, trifluoroacetic acid (80.16 mg, 0.05 mL, 0.71 mmol) was added dropwise. The internal temperature of the reaction was maintained below -20 °C. After 20 minutes saturated aqueous solution of NaHCO₃ was added, the reaction mixture was stirred for 10 minutes. The layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-3%) to yield alkyne **1.11** (Rf: 0.6 hexanes/EtOAc 2%, 52.2 mg 41% over two steps) ¹H NMR (400 MHz, CDCl₃) δ 7.68 (td, J = 7.8, 1.5 Hz, 4H), 7.45 – 7.35 (m, 6H), 3.85 (dt, J = 12.7, 6.8 Hz, 1H), 3.77 (dd, J = 10.4, 4.5 Hz, 1H), 3.70 – 3.62 (m, 3H), 2.31 (t, J = 7.1 Hz, 2H), 2.13 – 2.01 (m, 2H), 1.74 – 1.68 (m, 2H), 1.30 – 1.20 (m, 1H), 1.11 (dd, J = 12.3, 6.6 Hz, 1H), 1.06 (s, 9H), 0.88 (s, 9H), 0.06 – 0.01 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 135.84, 135.75, 133.78, 133.66, 129.75, 127.76, 84.31, 79.51, 78.63, 65.73, 61.80, 58.49, 32.17, 31.81, 26.98, 26.08, 24.46, 19.41, 19.26, 18.46, 15.57, -5.19. HRMS (ESI⁺) *m/z* calcd for C₃₃H₄₉O₃Si₂ (M+H)⁺: 549.3215 found 549.3213.

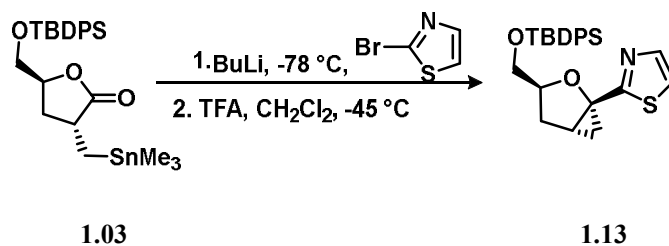


2-((1*R*,3*S*,5*S*)-3-(((*Tert*-Butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-

yl)benzothiazole (1.12) To a solution of benzothiazole (81.00 mg, 0.49 mmol) in THF (3.0 mL) at -78 °C, a solution of *n*-BuLi (2.5 M, 0.55 mmol, 0.22 mL) was added dropwise over a period of 10 min, after completion of addition, the reaction was stirred for 1h, transferred dropwise via cannula to a flask containing a solution of lactone **1.03** (202 mg, 0.38 mmol) in THF (1.50 mL) at -78 °C. The reaction was quenched by addition of pH 7 buffer solution. The cold reaction mixture was diluted with EtOAc (20 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

To the resulting crude lactol in CH₂Cl₂ (6 mL) at -45 °C, trifluoroacetic acid (54.00 mg, 0.473 mmol, 0.04 mL) was added dropwise. The internal temperature of the reaction was maintained below -20 °C. After 20 minutes a saturated aqueous solution of NaHCO₃ was added, stirred for 10 minutes. The layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-5%) to yield thiazole **1.12** (Rf: 0.5 hexanes/ EtOAc 2%, 129 mg, 70% over two steps) as an oil. ¹H NMR (300 MHz, CDCl₃) δ 7.88 (dd, *J* = 15.2, 7.9 Hz,

2H), 7.80 – 7.67 (m, 4H), 7.48 – 7.28 (m, 8H), 4.30 – 4.18 (m, 1H), 3.88 – 3.76 (m, 2H), 1.98 – 1.88 (m, 1H), 1.56 (t, $J = 5.7$ Hz, 1H), 1.07 (d, $J = 6.4$ Hz, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 173.09, 153.55, 135.81, 135.80, 135.14, 133.56, 129.85, 127.87, 127.84, 125.97, 124.25, 122.35, 121.63, 81.99, 70.44, 65.21, 31.76, 29.27, 26.95, 22.36, 19.40. HRMS (ESI^+) m/z calcd for $\text{C}_{29}\text{H}_{32}\text{NO}_2\text{SSi}$ ($\text{M}+\text{H}$) $^+$ 486.1917 found 486.1936

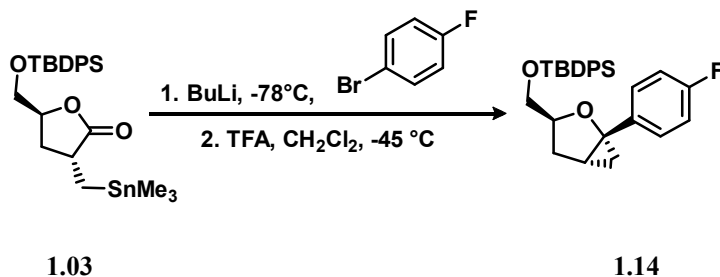


2-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-

yl)thiazole To a stirring solution of 2-Bromothiazole (67.00 mg, 0.04 mL, 0.41 mmol) in THF (5.0 mL) at -78°C , *n*-BuLi (2.50 M in hexanes, 0.17 mL, 0.41 mmol) was added dropwise over a period of 10 min, transferred dropwise via cannula to a flask containing a solution of lactone **1.03** (156.00 mg, 0.29 mmol) in THF (1.0 mL) at -78°C . The reaction was quenched by addition of a pH 7 buffer solution. The cold reaction mixture was diluted with EtOAc (40 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure.

To the resulting crude lactol in CH_2Cl_2 (15.40 mL) at -45°C , trifluoroacetic acid (0.22 mL, 335.00 mg, 2.9 mmol) was added dropwise. The internal temperature of the reaction was

maintained below -20 °C. After 20 minutes saturated aqueous solution of NaHCO₃ was added, the reaction mixture was stirred for 10 minutes. The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (10%) to yield thiazole **1.13** (102 mg, 80 % over two steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.69-7.75 (m, 4H), 7.80 – 7.67 (d, *J* = 3.3 Hz, 1H), 7.48 – 7.28 (m, 6H), 7.21 (d, *J* = 3.33 Hz, 1H) 4.30 – 4.18 (m, 1H), 3.82 (dd, *J* = 4.3 Hz, *J* = 10.9 Hz, 1H), 3.77 (dd, *J* = 4.7 Hz, *J* = 10.9 Hz, 1H), 2.27 (1H, m) 2.09-2.16 (2H, m), 1.77 (ddd, *J* = 0.9 Hz, *J* = 6.1 Hz *J* = 9.1 Hz, 1H), 1.48 (t, *J* = 5.8 Hz, 1H). 1.06 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 171.50, 142.00, 135.54, 135.52, 133.30, 133.28, 129.60, 125.97, 127.61, 127.58, 117.80, 81.10, 70.20, 64.90, 31.50, 27.80, 26.70, 20.9, 19.1. HRMS (ESI⁺) *m/z* calcd for C₂₅H₃₀NO₂SSi (M+H)⁺ 436.1761 found 436.1777, C₂₅H₂₉NaNO₂SSi (M+Na)⁺ 458.1581 found 458.1580

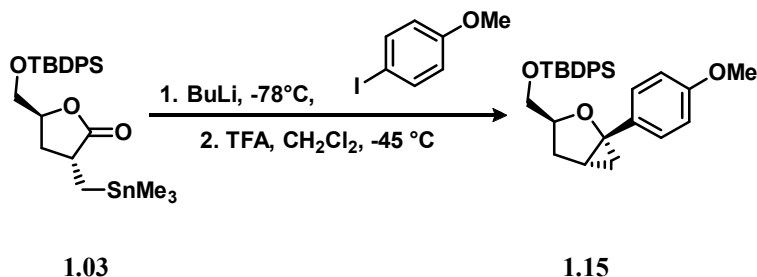


***tert*-butyl(((1*R*,3*S*,5*S*)-1-(4-fluorophenyl)-2-oxabicyclo[3.1.0]hexan-3**

yl)methoxy)diphenylsilane (1.14). To a solution of 1-bromo-4-fluorobenzene (104.53 mg, 0.60 mmol) in THF (4.0 mL) *n*-BuLi (38.26 mg 2.50 M 0.24 mL) was added dropwise over a period of 10 min, after completion of addition, the reaction was stirred for 2h, transferred it dropwise

via cannula to a flask containing a solution of the TBDPS protected lactone **1.03** (105.80 mg, 0.2 mmol) in THF (2.3 mL) at -78 °C for 1 h and warmed slowly to -45 °C, stirred for 1h. Quenched with pH 7 buffer solution. The cold reaction mixture was diluted with EtOAc (30 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

To the crude hemiacetal in CH₂Cl₂ (9.0 mL) at -45 °C, trifluoroacetic acid (68.11 mg, 0.05 mL, 0.60 mmol) was added dropwise. The internal temperature of the reaction was maintained below -20 °C. After 30 minutes saturated aqueous solution of NaHCO₃ was added, the reaction mixture was stirred for 10 minutes. The aqueous phase was extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-2.5%) to yield **1.14** (Rf: 0.6 hexanes/ EtOAc 2%, 31.10 mg, 35% over two steps). ¹H NMR (300 MHz, CDCl₃) δ 7.69 – 7.64 (m, 4H), 7.44 – 7.30 (m, 6H), 7.26 (s, 2H), 7.00 – 6.91 (m, 2H), 4.12 – 3.97 (m, 1H), 3.74 (d, *J* = 4.6 Hz, 2H), 2.22 – 2.03 (m, 2H), 1.66 (dt, *J* = 9.7, 4.9 Hz, 1H), 1.27 (dd, *J* = 11.4, 6.0 Hz, 1H), 1.09 (dd, *J* = 9.0, 6.5 Hz, 1H), 1.03 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 135.79, 133.72, 129.78, 127.79, 126.82, 126.74, 115.09, 114.88, 79.73, 69.46, 65.65, 32.07, 26.95, 25.18, 19.42, 18.25. ¹⁹F NMR (282 MHz, CDCl₃) δ -118.26 (tt, *J* = 8.7, 5.4 Hz).. HRMS (ESI⁺) *m/z* calcd for C₂₈H₃₂FO₂Si (M+H)⁺ 447.2150 found 447.2150

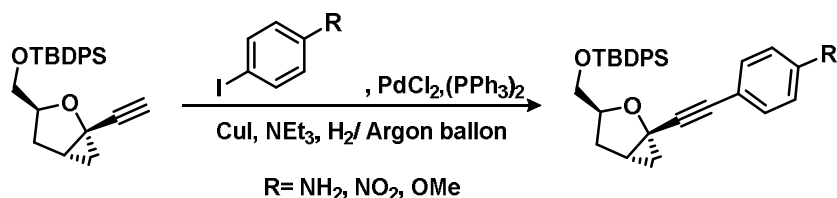


***tert*-butyl(((1*R*,3*S*,5*S*)-1-(4-methoxyphenyl)-2-oxabicyclo[3.1.0]hexan-3-**

yl)methoxy)diphenylsilane) (1.15). To a solution of 1-iodo-4-methoxybenzene (135.00 mg, 0.60 mmol) in THF (5.80 mL) *n*-BuLi (36.89 mg 2.50 M 0.23 mL) was added dropwise over a period of 20 min. The reaction was stirred for 1h. Transferred dropwise via cannula to a flask containing a solution of the TBDPS protected lactone **1.03** (102.00 mg, 0.19 mmol) in THF (3.80 mL) at -78 °C, stirred for 1 h and let it warm to -45 °C, stirred for 1 hour. Quenched with pH 7 buffer solution. The cold reaction mixture was diluted with EtOAc (20 mL). The layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

To the crude lactol in CH₂Cl₂ (9.0 mL) at -45 °C, trifluoroacetic acid (65.66 mg, 0.05 mL, 0.58 mmol) was added dropwise. The internal temperature of the reaction was maintained below -20 °C, the reaction progress was monitored by TLC. After 30 minutes saturated aqueous solution of NaHCO₃ was added, the reaction mixture was stirred for 10 minutes. The layers were separated. The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-2.5%) to yield the desired product **1.15** (Rf: 0.6 hexanes/EtOAc 2%, 35.20 mg, 40% over

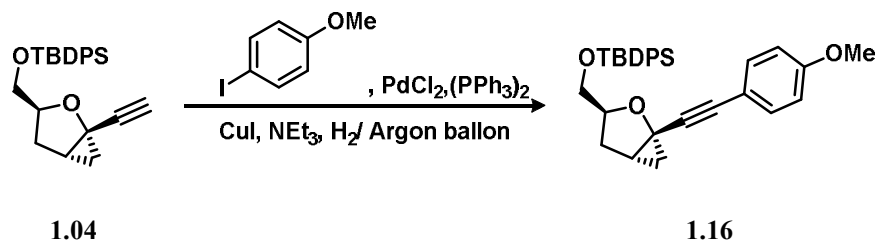
two steps). ^1H NMR (300 MHz, CDCl_3) δ 7.74 – 7.68 (m, 4H), 7.40 (ddd, J = 8.6, 6.2, 2.0 Hz, 6H), 7.30 – 7.26 (m, 2H), 6.93 – 6.82 (m, 2H), 4.12 – 4.03 (m, 1H), 3.80 (s, 3H), 3.78 (dd, J = 4.8, 2.7 Hz, 2H), 2.21 – 2.12 (m, 2H), 1.70 – 1.61 (m, 1H), 1.27 (dd, J = 6.3, 5.2 Hz, 1H), 1.09 (d, J = 2.2 Hz, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ 158.51, 135.79, 133.76, 132.93, 129.74, 127.78, 126.72, 113.67, 79.43, 69.66, 65.75, 55.46, 32.25, 26.96, 24.56, 19.41, 17.51. HRMS (ESI $^+$) m/z calcd for $\text{C}_{29}\text{H}_{35}\text{O}_3\text{Si}$ ($\text{M}+\text{H}$) $^+$ 459.2350 found 459.2337, $\text{C}_{29}\text{H}_{38}\text{NO}_3\text{Si}$ ($\text{M}+\text{NH}_4$) $^+$ 476.2615 found 476.2613.



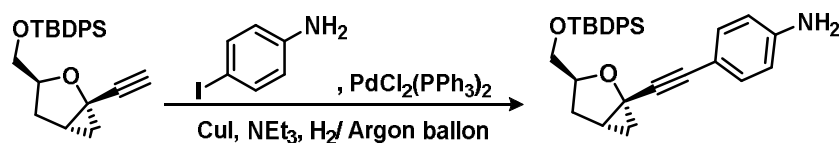
1.04

General procedure 1

The procedure for the Sonogashira coupling was followed as reported by Tong-Ing Ho, 2003.⁴⁶ A flask containing, the aryl halide (1 eq), dichlorobis(triphenylphosphine)palladium(II), the catalyst, (1 mol %) and CuI (1 mol) was degassed and back-filled three times with a mixture of hydrogen and argon from a balloon. Triethylamine was added to the reaction mixture using a syringe under the gaseous mixture atmosphere. Then, the alkyne derivative **1.04** (1 eq) was added using a syringe. After the reaction was complete by TLC, the volatiles were removed under reduced pressure. The residue was partitioned between EtOAc and a saturated aqueous solution of NaHCO_3 . The layers were separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure.

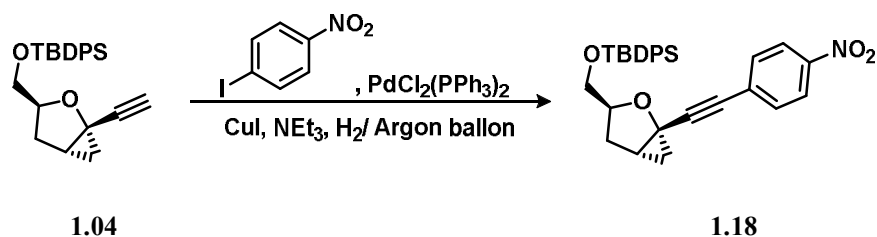


***tert*-Butyl(((1*R*,3*S*,5*S*)-1-((4-methoxyphenyl)ethynyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)diphenylsilane (**1.16**).** According to the general procedure **1** to a flask containing 4-iodoanisole (8.79 mg, 0.04 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.26 mg, 3.70 x10⁻⁴ mmol) and CuI (0.07 mg, 3.70 x10⁻⁴ mmol) in triethylamine (0.1 mL), was added dropwise, the alkyne derivative **1.04** (14.00mg, 0.04 mmol) in triethylamine (0.1mL). The reaction was completed after 24 h at r.t. Worked-up was performed as described in the general procedure **1**. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-5%) to yield the desired bicycle **1.16** (Rf: 0.4 hexanes/EtOAc 10%, 10.00 mg 56%). ¹H NMR (300 MHz, CDCl₃) δ 7.78 – 7.61 (m, 5H), 7.44 – 7.31 (m, 8H), 6.85 – 6.77 (m, 1H), 3.97 – 3.85 (m, 1H), 3.80 (s, 3H), 3.77 (m, 1H), 3.70 (m, 1H), 2.24 – 1.98 (m, 2H), 1.94 – 1.81 (m, 1H), 1.24 – 1.20 (m, 1H), 1.06 (s, 9H), 0.92 – 0.85 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 135.88, 135.78, 133.39, 129.77, 127.78, 113.94, 83.80, 79.94, 65.64, 58.69, 55.39, 32.02, 29.85, 26.99, 25.25, 20.08, 19.44. HRMS (ESI⁺) *m/z* calcd for: C₃₁H₃₅O₃Si (M+H)⁺: 483.2350 found 483.2355.



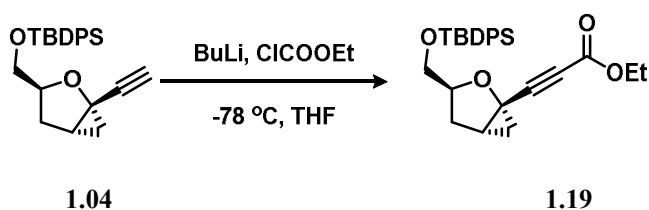
4-(((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-

yl)ethynyl)aniline (1.17) According to the general procedure **1** to a flask containing 4-iodoaniline (9.89 mg, 0.05 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.32 mg, 4.50×10^{-4} mmol) and CuI (0.09 mg 4.50×10^{-4} mmol) in triethylamine (0.15 mL), Then alkyne **1.04** (14.00mg, 0.04 mmol) in triethylamine (0.20 mL) was added dropwise. The reaction was stirred overnight. After worked-up as described in the general procedure **1**, the reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-5%) to yield the aniline **1.17** (Rf 0.4 hexanes /EtOAc 10%, 12.50 mg, 60 %). ^1H NMR (400 MHz, CDCl_3) δ 7.74 – 7.64 (m, 4H), 7.43 – 7.33 (m, 6H), 7.24 – 7.18 (m, 2H), 6.59 – 6.52 (m, 2H), 3.91 (ddd, $J = 15.5, 7.7, 5.3$ Hz, 1H), 3.79 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.69 (dd, $J = 10.5, 5.5$ Hz, 1H), 2.17 (ddd, $J = 13.2, 8.9, 4.9$ Hz, 1H), 2.12 – 2.06 (m, 1H), 1.90 – 1.82 (m, 1H), 1.22 (d, $J = 5.8$ Hz, 1H), 1.07 (s, $J = 2.9$ Hz, 9H), 1.03 (dd, $J = 4.1, 2.0$ Hz, 1H). HRMS (ESI $^+$) m/z calcd for: $\text{C}_{30}\text{H}_{34}\text{NO}_2\text{Si}$ ($\text{M}+\text{H}$) $^+$ 468.2353 found 468.2367, $\text{C}_{30}\text{H}_{33}\text{NNaO}_2\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 490.2173 found 490.2181.

***tert*-Butyl(((1*R*,3*S*,5*S*)-1-((4-nitrophenyl)ethynyl)-2-oxabicyclo[3.1.0]hexan-3-**

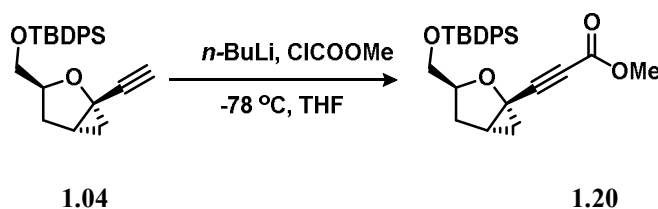
yl)methoxy)diphenylsilane (1.18). According to the general procedure **1**, to a flask containing 1-iodo-4-nitrobenzene (11.57 mg, 0.05 mmol), dichlorobis(triphenylphosphine)palladium(II) (0.33 mg, 4.60×10^{-4} mmol) and CuI (0.09 mg, 4.60×10^{-4} mmol) in triethylamine (0.15 mL), the

alkyne derivative **1.04** (14.00 mg, 0.04.1mmol) in triethylamine (0.15 mL) was added dropwise. The reaction was completed after 1 h at r.t. After worked-up as described in the general procedure **1**, the reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-5%) to yield the desired bicycle **1.18** (Rf 0.4 hexanes/EtOAc 10%), 14.50 mg, 78%). ¹H NMR (300 MHz, CDCl₃) δ 8.19 – 8.12 (m, 2H), 7.74 – 7.64 (m, 4H), 7.55 – 7.46 (m, 2H), 7.43 – 7.34 (m, 6H), 4.03 – 3.91 (m, 1H), 3.79 – 3.69 (m, 2H), 2.32 – 2.17 (m, 1H), 2.16 – 2.05 (m, 1H), 2.06 – 1.94 (m, 1H), 1.46 – 1.37 (m, 1H), 1.21 – 1.11 (m, 1H), 1.08 – 0.95 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 146.99, 135.84, 135.75, 133.66, 133.54, 132.26, 129.82, 127.81, 127.79, 123.64, 94.12, 82.43, 80.77, 65.43, 58.48, 31.71, 26.96, 26.22, 21.13, 19.44..HRMS (ESI⁺) *m/z* calcd for: C₃₀H₃₅N₂O₄Si (M+ NH₄)⁺ 515.2361 found 515.2373.



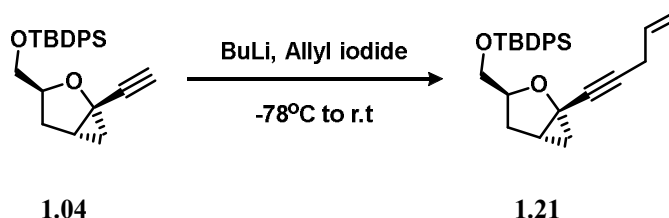
Ethyl 3-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-yl)propiolate (1.19**).** To a solution of alkyne derivative **1.04** (20.00 mg, 0.05 mmol) in THF (1 mL) at -78 °C, *n*-BuLi in hexanes (2.5 M, 0.02 mL, 0.06 mmol) was added dropwise over 10 min. After complete addition, the reaction was stirred at -78 °C for 15 minutes and became yellow. Ethyl chloroformate (17.83 mg, 0.16 mmol) was added in one portion to the reaction which was stirred for 10 min, turning to a white color. The reaction was quenched with a saturated solution of NH₄Cl. The organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash

chromatography eluting with hexanes containing EtOAc (0-5%) to yield the desired ester **1.19** (Rf: 0.4 hexanes/ EtOAc 5%, 23.20 mg, 98%). ^1H NMR (300 MHz, CDCl_3) δ 7.69 (ddd, J = 7.6, 5.2, 2.1 Hz, 4H), 7.49 – 7.34 (m, 6H), 4.22 (q, J = 7.1 Hz, 2H), 4.02 – 3.89 (m, 1H), 3.75 – 3.65 (m, 2H), 2.26 – 2.12 (m, 1H), 2.03 (ddd, J = 11.4, 10.5, 6.6 Hz, 2H), 1.35 – 1.25 (m, 4H), 1.24 – 1.15 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 153.60, 135.84, 135.77, 133.57, 133.44, 129.81, 127.82, 87.25, 81.20, 65.27, 61.99, 57.64, 31.38, 26.95, 21.75, 19.39, 14.17. HRMS (ESI^+) m/z calcd for $\text{C}_{27}\text{H}_{36}\text{NO}_4\text{Si}$ ($\text{M}^+ \text{NH}_4$) $^+$ 466.2408 found 466.24161 $\text{C}_{27}\text{H}_{32}\text{O}_4\text{SiNa}$ ($\text{M}^+ \text{Na}$) $^+$ 471.1962 found 471.1971.



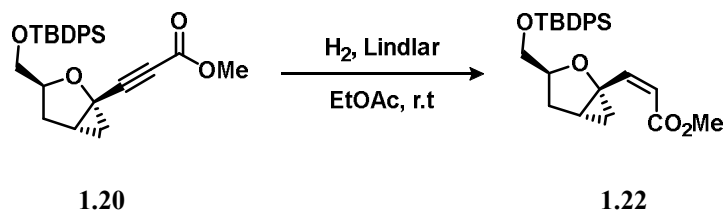
Methyl 3-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-yl)propionate (1.20) Methyl ester **1.20** was synthesized according to the procedure to obtain ester **1.19**. To a solution of the alkyne derivative **1.04** (44.20 mg, 0.12 mmol) in THF (1.7 mL) at -78 °C, $n\text{-BuLi}$ in hexanes (2.5 M, 0.14 mmol, 0.06 mL). The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (0-5%) to yield the desired product **1.20** (Rf: 0.6 hexanes 10% EtOAc, 42.85 mg, 84%). ^1H NMR (300 MHz, CDCl_3) δ 2.42 – 2.34 (m, 4H), 2.15 – 2.03 (m, 6H), -1.37 (ddd, J = 15.2, 7.8, 4.6 Hz, 1H), -1.55 (s, 3H), -1.62 (dd, J = 4.6, 1.3 Hz, 2H), -3.06 – -3.19 (m, 1H), -3.22 – -3.33 (m, 2H), -4.03 (t, J = 6.1 Hz, 1H), -4.13 (ddd, J = 9.0, 6.2, 0.8 Hz, 1H), -4.25 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.00, 135.84, 135.76, 133.56, 133.42, 129.82, 127.81, 87.78, 81.22, 65.21, 57.60, 52.72,

31.34, 26.94, 21.80, 19.38. HRMS (ESI⁺) m/z calcd for C₂₆H₃₄NO₄Si (M+NH₄)⁺ 452.2252 found 452.2264.



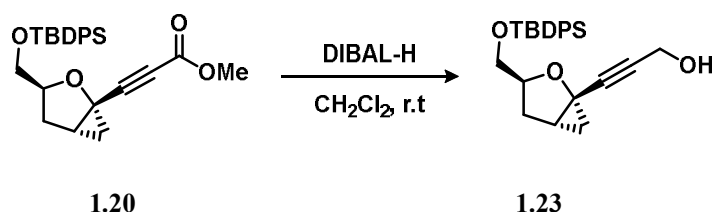
***Tert*-Butyl(((1*R*,3*S*,5*S*)-1-(pent-4-en-1-yn-1-yl)-2-oxabicyclo[3.1.0]hexan-**

3yl)methoxy)diphenylsilane (1.21) To a solution of the alkyne derivative **1.04** (16.00 mg, 0.04 mmol) in THF (1 mL) at -78 °C, *n*-BuLi in hexanes (2.5 M, 0.05 mmol, 0.02 mL) was added dropwise over 10 min, after completion of addition, the reaction was stirred at the same temperature for 15 minutes, then, allyl iodide (0.04 mL, 0.05 mmol) was added slowly, the reaction was stirred at -78 °C for 30 min and then allowed to warm slowly to r.t. The reaction was quenched with a saturated solution of NH₄Cl. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. (Rf: 0.7 Hexanes/ EtOAc 10%). The crude was submitted without purification to the deprotection step.



Methyl (Z)-3-(((1R,3S,5S)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2-

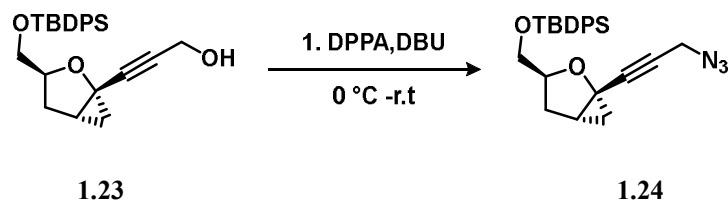
oxabicyclo[3.1.0]hexan-1-yl)acrylate (1.22) A solution of the ester **1.20** (38.00 mg, 0.09 mmol), quinoline (0.02 mL, 0.17 mmol), and commercially available Lindlar catalyst (11.17 mg) in EtOAc (1 mL), the mixture was stirred under 1 atm of H₂ overnight. The solution was filtered through Celite® which was washed with H₂O, saturated aqueous solution of NaHCO₃, and brine. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure, to give **1.22** as a colorless oil. HRMS (ESI⁺) *m/z* calcd for C₂₆H₃₃O₄Si (M+H)⁺ 437.21426 found 437.2152, C₂₆H₃₂NaO₄S (M+Na)⁺ 459.1962 found 459.1964



3-(((1R,3S,5S)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-

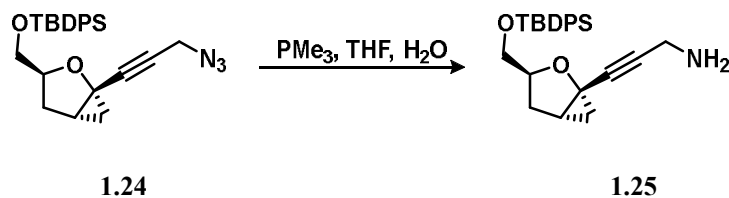
yl)prop-2-yn-1-ol (1.23) To a stirring solution of the methyl ester **1.20** (22.40 mg, 0.05 mmol) in dichloromethane (0.3 mL) at -78 °C. DIBAL-H (0.10 mL as a 1.0 M solution in DCM, 0.10 mmol, 2.2 eq) was added dropwise and the mixture was stirred for 15 min. A saturated solution of Rochelle's salt was added to the cooled reaction mixture, which was allowed to warm to r.t. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL).

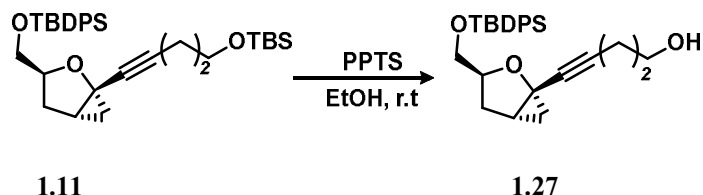
The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with hexanes containing 20 % EtOAc, to obtain a mixture containing as a major the aldehyde product 17.5 mg, which was resubmitted to the same conditions. The residue was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (20%) to yield the alcohol **1.23** (17.0 mg, 80 % over two steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.72 – 7.64 (m, 4H), 7.46 – 7.34 (m, 6H), 4.29 (d, *J* = 3.0 Hz, 2H), 3.89 (tt, *J* = 7.2, 4.7 Hz, 1H), 3.74 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.66 (dd, *J* = 10.5, 5.4 Hz, 1H), 2.18 – 2.02 (m, 2H), 1.85 – 1.78 (m, 1H), 1.17 (t, *J* = 5.9 Hz, 1H), 1.05 (d, *J* = 2.8 Hz, 9H), 1.02 – 0.96 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 135.79, 135.73, 133.61, 133.59, 129.78, 127.77, 127.75, 84.61, 82.63, 80.12, 65.62, 58.08, 51.32, 31.88, 26.95, 25.03, 19.96, 19.39. HRMS (ESI⁺) *m/z* calcd for C₂₅H₃₄NO₃Si (M+NH₄)⁺ 424.2302 found 424.2303.



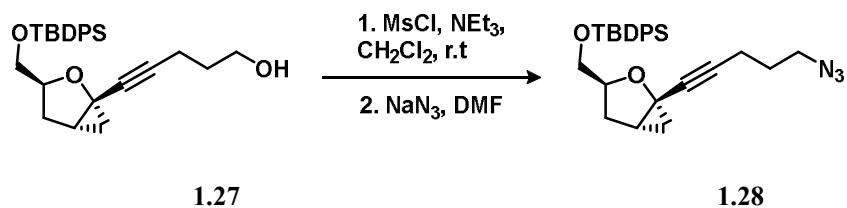
(((1*R*,3*S*,5*S*)-1-(3-azidoprop-1-yn-1-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(tert-butyl)diphenylsilane (1.24). To a stirring solution of the terminal alcohol **1.23** (43.40 mg, 0.11 mmol) in THF (1.0 mL) DPPA (40.14 mg, 0.16 mmol, 0.03 mL) and DBU (24.87 mg, 0.16 mmol, 0.02 mL) were added dropwise at 0 °C. The reaction mixture was allowed to warm to r.t and stirred overnight. Saturated aqueous solution of NH₄Cl was added. The organic layer was separates. The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue

was purified by silica gel flash chromatography eluting with hexanes containing EtOAc (20 %). Evaporation of the collected fraction gave azide **1.24** (40.0 mg, 86 %) as colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 7.78 – 7.62 (m, 4H), 7.47 – 7.34 (m, 6H), 3.99 – 3.86 (m, 3H), 3.71 (qd, J = 10.6, 4.9 Hz, 2H), 2.21 – 2.10 (m, 1H), 2.10 – 2.01 (m, 1H), 1.85 (dt, J = 9.3, 5.4 Hz, 1H), 1.22 (dd, J = 10.5, 4.5 Hz, 1H), 1.09 – 0.97 (m, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ 135.83, 135.75, 133.68, 133.56, 129.79, 127.79, 127.77, 86.55, 80.38, 76.30, 65.44, 57.92, 40.38, 31.77, 26.96, 25.50, 20.41, 19.41. HRMS (ESI^+) m/z calcd for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{NaO}_2\text{Si}$ ($\text{M}+\text{Na}$) $^+$ 454.1921 found 454.1926. IR $\nu_{\text{max}}/\text{cm}^{-1}$: 2117.99 ($\text{R}-\text{N}_3$)





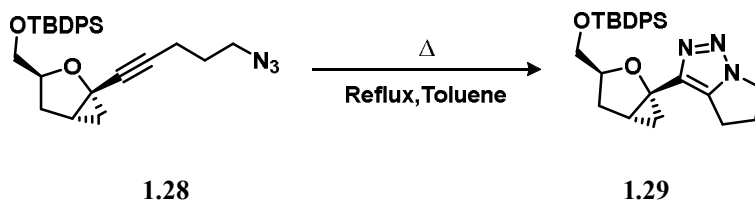
5-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-yl)pent-4-yn-1-ol (1.27) To the alkyne **1.11** (58.00 mg, 0.11 mmol) in ethanol (0.6 mL), pyridinium *p*-toluenesulfonate (56.90 mg, 0.22 mmol) was added at room temperature, the reaction was stirred for 8 h. The volatiles were removed under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing (10-25% EtOAc to yield the desired product **1.27** (Rf: 0.2 EtOAc/hexanes 2:8, 36.20 mg 78%). ¹H NMR (400 MHz, CDCl₃) δ 7.67 (dd, *J* = 11.4, 4.5 Hz, 4H), 7.39 (tt, *J* = 8.1, 4.2 Hz, 6H), 3.89 – 3.81 (m, 1H), 3.78 – 3.69 (m, 3H), 3.69 – 3.62 (m, 1H), 2.35 (t, *J* = 6.9 Hz, 2H), 2.16 – 2.00 (m, 2H), 1.77 – 1.69 (m, 3H), 1.12 (t, *J* = 5.7 Hz, 1H), 1.06 (s, 9H), 0.90 (dd, *J* = 8.9, 6.2 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 135.85, 135.76, 133.67, 129.77, 127.77, 125.38, 80.96, 65.44, 61.93, 58.42, 37.48, 32.06, 31.35, 26.98, 24.54, 19.42, 15.70. HRMS (ESI⁺) *m/z* calcd for C₂₇H₃₈NO₃Si (M⁺ NH₄)⁺ 452.2616 found 452.2630



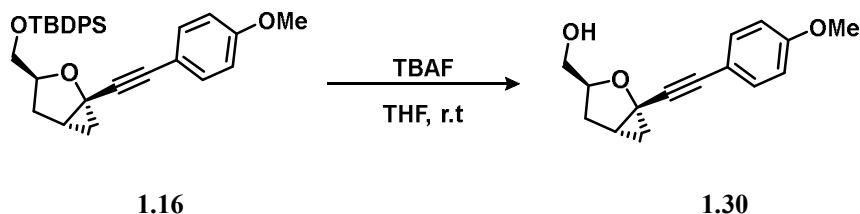
(((1*R*,3*S*,5*S*)-1-(5-azidopent-1-yn-1-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(*tert*-butyl)diphenylsilane (1.28) To a stirring solution of alcohol **1.27** (80.00 mg, 0.18 mmol) and NEt₃ (0.39 mmol, 0.051 mL) in DCM (0.7 mL), MeSO₂Cl (0.04 mL, 0.55 mmol) was added at r.t. The reaction mixture was washed with HCl, diluted with EtOAc. The organic layer was separated and washed with a saturated solution of NaHCO₃. The aqueous layer was extracted

with EtOAc (2 X 50 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. To provide the corresponding Mesylate: NMR ¹H NMR (400 MHz, CDCl₃) δ 7.67 (td, *J* = 7.7, 1.5 Hz, 4H), 7.46 – 7.34 (m, 6H), 4.34 – 4.26 (m, 2H), 3.85 (ddd, *J* = 12.7, 7.7, 5.1 Hz, 1H), 3.73 (dt, *J* = 11.3, 5.7 Hz, 1H), 3.68 – 3.62 (m, 1H), 3.12 (qd, *J* = 7.3, 4.9 Hz, 2H), 2.97 (s, 3H), 2.39 (t, *J* = 6.8 Hz, 2H), 2.13 – 2.01 (m, 2H), 1.91 (p, *J* = 6.5 Hz, 2H), 1.79 – 1.69 (m, 1H), 1.40 (t, *J* = 7.3 Hz, 2H), 1.13 (t, *J* = 5.8 Hz, 1H), 1.05 (s, 9H), 0.90 (dd, *J* = 9.0, 6.2 Hz, 1H).

The residue was taken up in DMF (1.5 mL), reacted with NaN₃ (24.05 mg, 0.37 mmol) and heated to 55 °C. The volatiles were removed under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting hexanes containing 20% of EtOAc to yield azide **1.28** (53.20 mg, 63% over two steps) ¹H NMR (300 MHz, CDCl₃) δ 7.71 – 7.64 (m, 4H), 7.45 – 7.34 (m, 6H), 3.85 (ddd, *J* = 12.5, 8.1, 5.5 Hz, 1H), 3.75 (dd, *J* = 10.4, 4.3 Hz, 1H), 3.66 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.37 (t, *J* = 6.7 Hz, 2H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.17 – 1.99 (m, 2H), 1.75 (tt, *J* = 9.4, 4.8 Hz, 3H), 1.13 (t, *J* = 5.8 Hz, 1H), 1.06 (s, 9H), 0.90 (dd, *J* = 8.8, 6.0 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 135.85, 135.76, 133.65, 129.78, 127.78, 124.69, 82.72, 79.70, 65.60, 58.51, 50.36, 32.02, 29.85, 27.92, 26.98, 24.62, 19.43, 16.46. HRMS (ESI⁺) *m/z* calcd for C₂₇H₃₃NaN₃O₂Si (M+Na)⁺ 482.2234 found 482.2233 IR *ν*_{max}/cm⁻¹: 2099.25 (R-N₃).



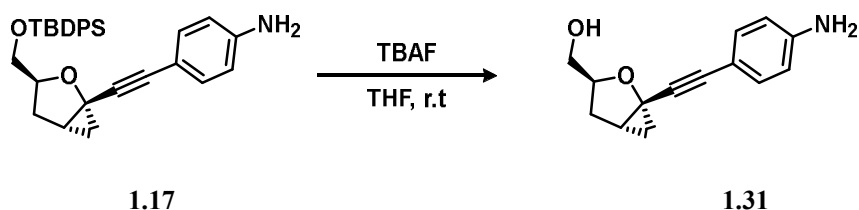
3-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-yl)-5,6 dihydro-4*H*-pyrrolo[1,2-*c*][1,2,3]triazole (1.29). The azide **1.28** (44.00 mg, 0.10 mmol) in toluene was refluxed for 36 hours. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography eluting with hexanes containing 20-50% EtOAc. To yield the triazole **1.29** (25.40 mg, 60 %) was isolated as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.69 – 7.62 (m, 4H), 7.44 – 7.29 (m, 6H), 4.24 (t, *J* = 7.3 Hz, 2H), 4.11 – 4.00 (m, 1H), 3.79 – 3.68 (m, 2H), 2.95 – 2.78 (m, 2H), 2.75 – 2.61 (m, 2H), 2.13 (dd, *J* = 7.7, 3.0 Hz, 2H), 1.91 (dd, *J* = 8.8, 5.3 Hz, 1H), 1.37 (dt, *J* = 6.9, 5.3 Hz, 1H), 1.26 (dd, *J* = 9.2, 3.3 Hz, 1H), 1.07 – 1.01 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) δ 135.70, 133.74, 133.57, 129.82, 129.76, 127.77, 79.93, 65.79, 65.12, 46.45, 32.18, 28.43, 26.93, 23.82, 21.28, 19.44, 17.76. HRMS (ESI⁺) *m/z* calcd for C₂₇H₃₄N₃O₂Si (M+H)⁺ 460.2415 found 460.2418.



((1*R*,3*S*,5*S*)-1-((4-methoxyphenyl)ethynyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol

(1.30). To a stirring solution of alkyne **1.16** (15.00 mg, 0.03 mmol) in THF (1.60 mL) at r.t. a solution of tetrabutylammonium fluoride (1 M in THF, 0.08 mL, 0.078 mmol) was added dropwise. The mixture was stirred for 5 hours. Diluted with EtOAc and treated with a saturated

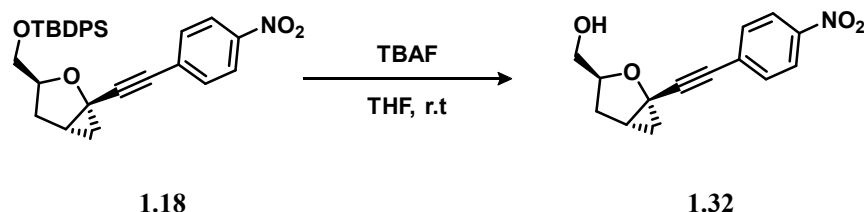
solution of NaHCO₃. The layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing 30%-40% of EtOAc to yield the alcohol **1.30** (Rf: 0.3 EtOAc/hexanes 6:4, 6.50 mg, 86%). ¹H NMR (300 MHz, CDCl₃) δ 7.45 – 7.32 (m, 2H), 6.87 – 6.79 (m, 2H), 3.98 – 3.87 (m, 1H), 3.80 (s, 3H), 3.75 (s, 1H), 3.64 – 3.53 (m, 1H), 2.22 – 2.11 (m, 1H), 2.05 – 1.88 (m, 3H), 1.31 – 1.24 (m, 1H), 1.11 – 1.04 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 159.66, 133.32, 114.69, 113.86, 85.72, 84.17, 79.50, 63.52, 58.41, 55.26, 30.24, 25.27, 19.22. HRMS (ESI⁺) *m/z* calcd for C₁₅H₁₇O₃ (M+H)⁺ 245.1172 found 245.1171



((1*R*,3*S*,5*S*)-1-((4-aminophenyl)ethynyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (1.31**)**

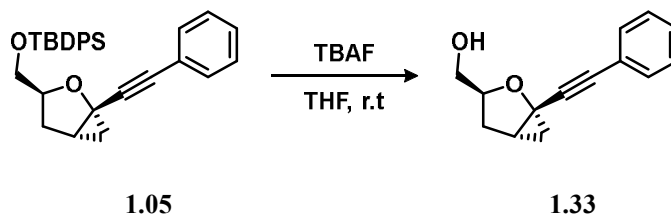
Alcohol **1.31** was synthesized according to the procedure to obtain alcohol **1.30**. Aniline **1.17** (12.00 mg, 0.03 mmol) in THF (1.30 mL), and tetrabutylammonium fluoride (1 M in THF, 0.06 mL, 0.06 mmol) was added. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing 40%-50% of EtOAc to yield alcohol **1.31** (Rf: 0.3 EtOAc/hexanes 1:1, 4.50 mg 76%). ¹H NMR (300 MHz, CDCl₃) δ 7.26 – 7.20 (m, 2H), 6.65 – 6.53 (m, 2H), 3.96 – 3.86 (m, 1H), 3.83 – 3.72 (m, 2H), 3.57 (dd, *J* = 11.9, 4.6 Hz, 1H), 2.24 – 2.09 (m, 1H), 2.09 – 1.95 (m, 2H), 1.99 – 1.84 (m, 2H), 1.30 – 1.23 (m, 1H), 1.09 – 1.00 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 146.85, 133.43, 114.76, 112.10, 84.99, 79.58, 77.36,

63.71, 58.66, 30.42, 25.36, 19.36. HRMS (ESI⁺) m/z calcd for C₁₄H₁₅NNaO₂ (M+Na)⁺ 252.0995 found 252.1004.

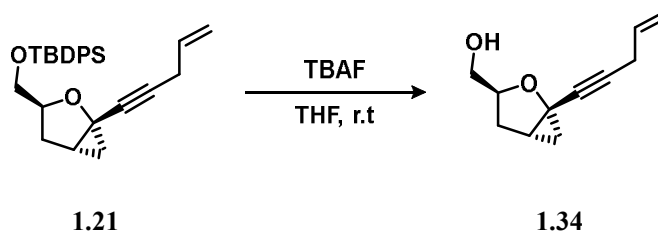


((1R,3S,5S)-1-((4-nitrophenyl) ethynyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (1.32).

Alcohol **1.32** was synthesized according to the procedure to obtain alcohol **1.30**. To a solution of the nitro **1.18** compound (22.00 mg, 0.04 mmol) in THF (2.20 mL) at r.t. a solution of tetrabutylammonium fluoride (1 M in THF, 0.11 mmol, 0.11 mL) was added dropwise. The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing 40%-50% of EtOAc to yield the desired product **1.32** (Rf: 0.4 EtOAc/hexanes 1:1, 10.20 mg 90%). ¹H NMR (300 MHz, CDCl₃) δ 8.21 – 8.14 (m, 2H), 7.61 – 7.53 (m, 2H), 4.01 – 3.91 (m, 1H), 3.79 (d, J = 11.8 Hz, 1H), 3.65 – 3.54 (m, 1H), 2.24 – 2.13 (m, 1H), 2.10 – 1.97 (m, 2H), 1.41 – 1.34 (m, 1H), 1.15 (ddd, J = 9.1, 6.4, 1.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 147.16, 132.38, 129.77, 123.70, 93.27, 82.81, 80.03, 63.54, 58.21, 30.30, 26.17, 19.91. HRMS (ESI⁺) m/z calcd for C₁₄H₁₄NO₄ (M+H)⁺ 260.0917 found 260.0918.



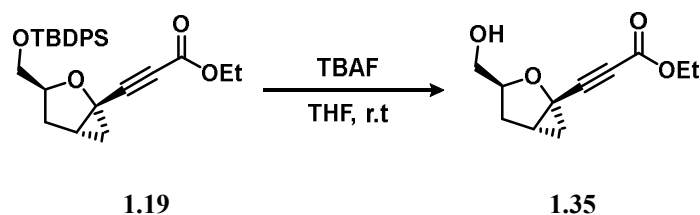
((1*R*,3*S*,5*S*)-1-(phenylethynyl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol. (1.33). Alcohol **1.33** was synthesized according to the procedure to obtain alcohol **1.30**. To a solution of the alkyne **1.05** (22.00 mg, 0.04 mmol) in THF (2.20 mL) at r.t a solution of tetrabutylammonium fluoride (1 M in THF, 0.11 mmol, 0.11 mL, 2.5 eq) was added dropwise. The residue was purified by silica gel flash chromatography eluting with hexanes containing 40%-50% of EtOAc to yield the desired product **1.33** (Rf: 0.4 EtOAc/hexanes 1:1, 10.20 mg, 90%). ¹H NMR (300 MHz, CDCl₃) δ 7.44 (dd, *J* = 6.7, 3.0 Hz, 2H), 7.34 – 7.27 (m, 3H), 3.98 – 3.85 (m, 1H), 3.78 (dd, *J* = 12.0, 2.9 Hz, 1H), 3.69 – 3.54 (m, 1H), 2.23 – 2.11 (m, 1H), 2.06 – 2.00 (m, 1H), 1.99 – 1.91 (m, 2H), 1.30 (dd, *J* = 12.2, 6.4 Hz, 1H), 1.10 (dd, *J* = 9.0, 6.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 131.88, 128.47, 128.38, 122.78, 87.37, 84.40, 79.78, 63.65, 58.47, 30.38, 25.56, 19.51. HRMS (ESI⁺) *m/z* calcd for C₁₄H₁₄NaO₂ (M⁺ Na)⁺ 237.0886 found 237.0889.



((1*R*,3*S*,5*S*)-1-(pent-4-en-1-yn-1-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (1.34)

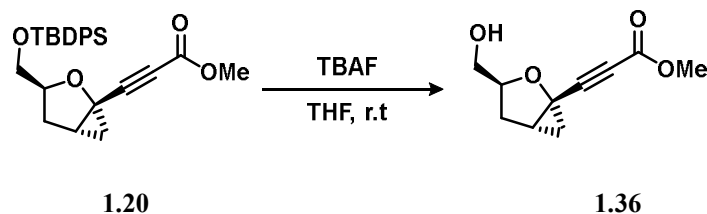
Alcohol **1.34** was synthesized according to the procedure to obtain alcohol **1.30**. To a solution of alkyne **1.21** (crude), 17.70 mg in THF (2.00 mL) at r.t. a solution of tetrabutylammonium fluoride (1 M in THF, 0.04 mmol, 0.04 mL) was added dropwise. The residue was purified by

silica gel flash chromatography eluting with Hexanes containing 20% of EtOAc to yield the desired alcohol **1.34** (Rf: 0.4 EtOAc/hexanes 2:8, 4.6 mg 60% over 2 steps). ^1H NMR (300 MHz, CDCl_3) δ 5.86 – 5.73 (m, 1H), 5.29 (dd, J = 17.0, 1.6 Hz, 1H), 5.11 (dd, J = 10.0, 1.6 Hz, 1H), 3.95 – 3.83 (m, 1H), 3.73 (d, J = 11.3 Hz, 1H), 3.57 (s, 1H), 3.03 (dt, J = 5.4, 1.7 Hz, 1H), 2.15 – 2.05 (m, 1H), 2.02 – 1.85 (m, 2H), 1.84 – 1.74 (m, 1H), 1.22 – 1.15 (m, 1H), 0.99 – 0.90 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 132.23, 116.29, 81.67, 79.40, 63.56, 58.21, 30.22, 29.69, 24.68, 23.31, 18.77. HRMS (ESI $^+$) m/z calcd for $\text{C}_{11}\text{H}_{14}\text{NaO}_2$ ($\text{M}+\text{Na}$) $^+$ 201.0886 found 201.08865.



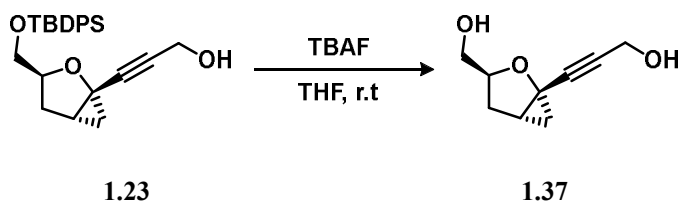
Ethyl 3-((1*R*,3*S*,5*S*)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)propiolate (1.35)

Alcohol **1.35** was synthesized according to the procedure to obtain alcohol **1.30**. To a stirring solution of **1.19** (25.70 mg, 0.06 mmol) in THF (0.85 mL) at r.t, a solution of tetrabutylammonium fluoride (1 M in THF, 0.06 mmol, 0.06 mL). The reaction residue was purified by silica gel flash chromatography eluting with hexanes containing 30% of EtOAc to yield the desired alcohol **1.35** (Rf: 0.4 EtOAc/hexanes 2:8, 8.50 mg, 71%). ¹H NMR (300 MHz, CDCl₃) δ 4.23 (q, *J* = 7.1 Hz, 2H), 3.99 – 3.88 (m, 1H), 3.73 (d, *J* = 11.7 Hz, 1H), 3.59 – 3.49 (m, 1H), 2.19 – 1.97 (m, 3H), 1.91 (s, 1H), 1.35 – 1.26 (m, 4H), 1.25 – 1.13 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 153.48, 86.57, 80.68, 76.94, 63.43, 62.17, 57.39, 30.11, 27.07, 20.78, 14.18. HRMS (ESI⁺) *m/z* calcd for C₁₁H₁₅O₄ (M+H)⁺ 211.0965 found 211. 0966.



Methyl 3-((1*R*,3*S*,5*S*)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)propiolate (1.36)

Alcohol **1.36** was synthesized according to the procedure to obtain alcohol **1.30**. To a solution of alkyne **1.20** (42.00 mg, 0.10 mmol) in THF (1.38 mL) at r.t. a solution of tetrabutylammonium fluoride (1 M in THF, 0.10 mmol, 0.10 mL) was added dropwise. The residue was purified by silica gel flash chromatography eluting with hexanes containing 30% of EtOAc to yield the desired alcohol **1.36** (Rf: 0.4 EtOAc/hexanes 2:8, 18.70 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ 3.97 – 3.90 (m, 1H), 3.77 (s, 3H), 3.76 – 3.70 (m, 1H), 3.54 (dd, *J* = 12.1, 4.9 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.08 – 1.90 (m, 3H), 1.34 (dd, *J* = 11.7, 5.5 Hz, 1H), 1.22 – 1.16 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 153.86, 87.13, 80.75, 76.59, 63.42, 57.35, 52.83, 30.12, 27.14, 20.86. HRMS (ESI⁺) *m/z* calcd for C₁₀H₁₆NO₄ 214.1074 (NH₄)⁺ found 214.1071.



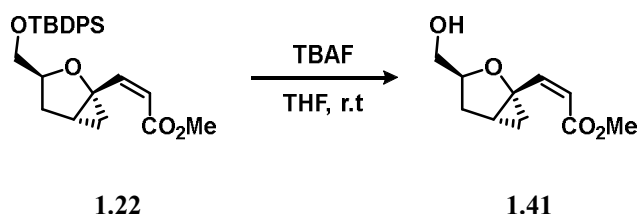
3-((1*R*,3*S*,5*S*)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)prop-2-yn-1-ol (1.37). To a stirring solution of **1.23** (10.00 mg, 0.024 mmol) in THF (0.5 mL) at r.t, a solution of tetrabutylammonium fluoride (1 M in THF, 0. 07 mL, 0.74 mmol) was added dropwise. The mixture was stirred for 6 hours. The solvent was removed under reduced pressure and the



((1*R*,3*S*,5*S*)-1-(thiazol-2-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (1.40)

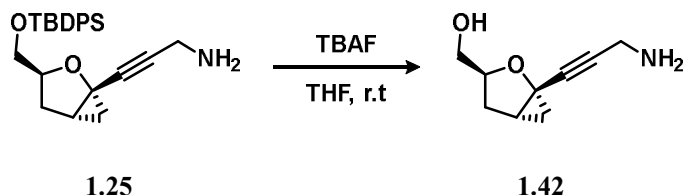
Alcohol **1.40** was synthesized according to the procedure to obtain alcohol **1.30**. To a solution of thiazole **1.13** (15.00 mg, 0.03 mmol) in THF (0.5 mL) at r.t a solution of tetrabutylammonium fluoride (1 M in THF, 0.09 mmol, 0.09 mL) was added dropwise. The residue was purified by

silica gel flash chromatography eluting EtOAc containing 50-20 % of hexanes to yield the alcohol **1.40** (5.70 mg, 85%). ^1H NMR (300 MHz, CDCl_3) δ 7.69 (d, J = 3.3 Hz, 1H), 7.22 (d, J = 3.3 Hz, 1H), 4.29 – 4.18 (m, 1H), 3.84 (dd, J = 12.1, 3.0 Hz, 1H), 3.60 (dd, J = 12.1, 4.9 Hz, 1H), 2.29 – 2.18 (m, 1H), 2.18 – 2.05 (m, 2H), 1.73 (ddd, J = 9.1, 6.2, 0.9 Hz, 1H), 1.46 (t, J = 5.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 171.36, 142.75, 117.89, 82.46, 70.01, 64.15, 31.15, 28.63, 21.95. HRMS (ESI^+) m/z calcd for $\text{C}_9\text{H}_{12}\text{NO}_2\text{S}$ ($\text{M}+\text{H}$) $^+$ 198.0583 found 198.0589, $\text{C}_9\text{H}_{11}\text{NaNO}_2\text{S}$ ($\text{M}+\text{Na}$) $^+$ 220.0403 found 270.0403.



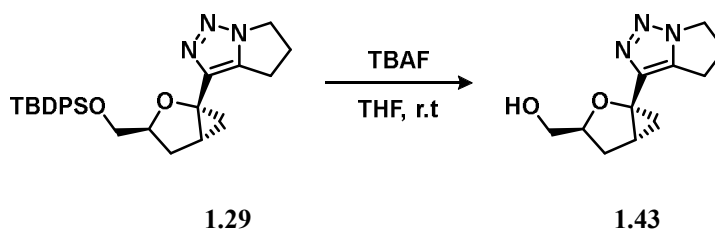
Methyl (Z)-3-((1R,3S,5S)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)acrylate (1.41)

Alcohol **1.41** was synthesized according to the procedure to obtain alcohol **1.30**. To a solution of alkene **1.22** (32.70 mg, 0.08 mmol) in THF (1.0 mL) at r.t, a solution of tetrabutylammonium fluoride (1 M in THF, 0.19 mmol, 0.19 mL, 2.50 eq) was added dropwise.. The residue was purified by silica gel flash chromatography eluting with Hexanes containing 35-40 % of EtOAc to yield the desired product **1.41** (13.20 mg, 89%) ^1H NMR (300 MHz, CDCl_3) δ 5.83 (d, J = 12.5 Hz, 1H), 5.68 (d, J = 12.5 Hz, 1H), 4.03 – 3.91 (m, 1H), 3.85 – 3.69 (m, 4H), 3.46 (t, J = 11.2 Hz, 1H), 2.42 – 2.30 (m, 1H), 2.04 – 1.95 (m, 1H), 1.92 – 1.82 (m, 1H), 1.24 (dd, J = 7.7, 4.0 Hz, 2H), 1.00 (ddd, J = 9.1, 6.3, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 169.19, 140.36, 118.24, 80.74, 68.02, 62.75, 52.05, 29.37, 26.13, 20.38. HRMS (ESI^+) m/z calcd for $\text{C}_{10}\text{H}_{14}\text{NaO}_4$ ($\text{M}+\text{Na}$) $^+$ 221.0784 found 221.0775.



((1*R*,3*S*,5*S*)-1-(3-aminoprop-1-yn-1-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methanol (1.42)

Alcohol **1.42** was synthesized according to the procedure to obtain alcohol **1.30**. To a solution of alkyne **1.25** (17.00mg, 0.04 mmol) in THF (0.9 mL) at r.t, a solution of tetrabutylammonium fluoride (1 M in THF, 0.11 mmol, 0.11 mL) was added dropwise. The mixture was stirred for 2 hours. The solvent was removed under reduced pressure and the reaction residue was purified by silica gel flash chromatography eluting with EtOAc containing 10% of NH₄OH to yield **1.42** (5.30 mg, 76%) ¹H NMR (400 MHz, CDCl₃) δ 3.92 – 3.80 (m, 1H), 3.73 (dd, *J* = 12.1, 2.8 Hz, 1H), 3.53 (dd, *J* = 12.1, 4.9 Hz, 1H), 2.75 (s, 3H), 2.10 (ddd, *J* = 15.9, 10.7, 6.2 Hz, 1H), 1.96 (dt, *J* = 12.3, 6.1 Hz, 1H), 1.80 (dt, *J* = 9.3, 5.5 Hz, 1H), 1.19 (t, *J* = 5.9 Hz, 1H), 0.98 – 0.92 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 81.04, 79.75, 77.36, 63.42, 58.03, 30.19, 29.84, 24.96, 18.84. HRMS (ESI⁺) *m/z* calcd for C₉H₁₄NO₂ (M+H)⁺ 168.1019 found 168.1027

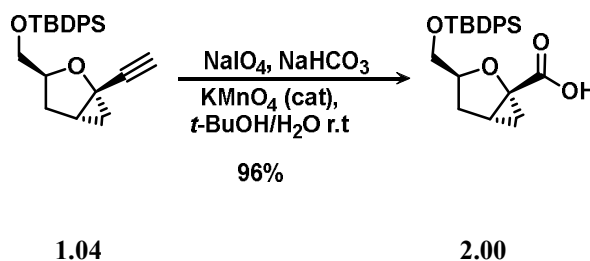


((1*R*,3*S*,5*S*)-1-(5,6-dihydro-4H-pyrrolo[1,2-*c*][1,2,3]triazol-3-yl)-2 oxabicyclo[3.1.0]hexan-3-yl)methanol (1.43) To a stirring solution of **1.29** (5.00 mg, 0.01 mmol) in THF (0.3 mL) at r.t a solution TBAF 1.0 M (4.27 mg, 1.0 M, 0.02 mL) was added dropwise. The reaction was complete after 1 hour. The volatiles were removed under reduced pressure. The reaction

residue was purified by silica gel flash chromatography eluting with hexanes/EtOAc (10-30%) to yield the desired product (2.20 mg, 91%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 4.31 (t, J = 7.3 Hz, 2H), 4.17 – 4.06 (m, 1H), 3.82 (dd, J = 12.0, 2.8 Hz, 1H), 3.57 (dd, J = 11.9, 4.7 Hz, 1H), 3.02 – 2.87 (m, 2H), 2.86 – 2.73 (m, 2H), 2.29 – 2.18 (m, 1H), 2.10 (dd, J = 12.3, 7.4 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.31 – 1.17 (m, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 139.48, 139.42, 81.63, 64.72, 64.29, 46.51, 31.41, 28.47, 24.29, 21.11, 18.61. HRMS (ESI^+) m/z calcd for HRMS (ESI^+) m/z calcd for $\text{C}_{11}\text{H}_{16}\text{N}_3\text{O}_2$ ($\text{M}+\text{H}$) $^+$ 222.1237 found 222.1234.

3.3 Experimental data chapter 2

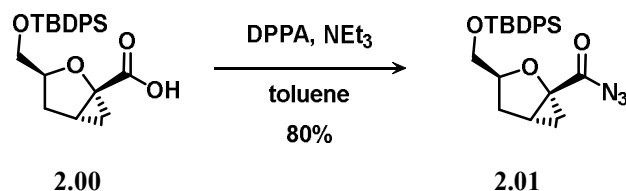
3.3.1. Synthesis of 1',2'-methano-2',3'-dideoxy-nucleosides 2.11, 2.14 and their phosphoramidate prodrug 2.20 and 2.21



(1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexane-1-

carboxylic acid (2.00) To a stirring solution of **1.04** (experimental data and procedure to obtain **1.04** are described on page IV.) (3.82 g, 10.09 mmol) in *t*-BuOH (336.37mL) NaIO₄ (13.08g, 60.55mmolmmol), was added, followed by dropwise addition of NaHCO₃ (1.16g, 13.81mmol) and KMnO₄ (174.5mg, 1.10mmol) in H₂O (110.5 mL) while the mixture was stirred vigorously. After stirring for 3 h, EtOH (20.0 mL) was added to the reaction, which was stirred for 10 minutes, filtered through a sintered glass funnel containing celite® , washed with *t*-BuOH (70 mL) and the filtrate was concentrated under reduced pressure to an approximate volume of 100 mL. The mixture was diluted with EtOAc and acidified with 1.0 M HCl. The layers were separated. The aqueous layer was extracted with EtOAc (3 x 70 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel flash chromatography eluting with hexane containing EtOAc (20%) to give acid **2.00** (3.80 g, 96%) as colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.73 – 7.63 (m, 4H), 7.50 – 7.35 (m, 6H), 4.18 – 4.07 (m, 1H), 3.73 (d, *J* = 4.8 Hz, 2H), 2.23 – 2.00 (m, 3H), 1.67 (dd, *J* = 9.5, 6.0 Hz, 1H), 1.30 (t, *J* = 5.7 Hz, 1H), 1.07 (s, 9H). ¹³C NMR (75

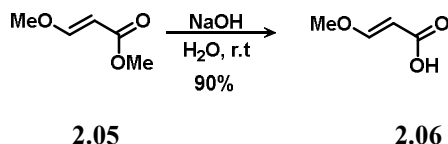
MHz, CDCl₃) δ 175.61, 135.63, 135.60, 133.14, 133.09, 129.84, 127.79, 83.45, 66.87, 64.87, 31.06, 28.26, 26.80, 22.55, 19.21. HRMS (ESI⁺) m/z calcd for C₂₃H₂₉O₄Si 397.1826 (M+H)⁺: found 397.1826, C₂₃H₃₂NO₄Si 414.2095 (M+NH₄)⁺ found: 414.2103.



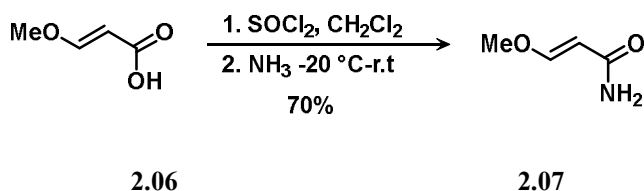
(1*R*,3*S*,5*S*)-3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexane-1-

carbonyl azide (2.01): To a stirring solution of the carboxylic acid **2.00** (3.80 g, 9.58 mmol) in toluene (240 mL) at 0 °C was added triethylamine dropwise (3.88 g, 5.31mL, 38.33mmol) followed by addition of diphenylphosphoryl azide (2.88 g, 2.25 mL, 11.50 mmol). The ice bath was removed and the reaction was stirred for 1 h at rt. After removing under reduced pressure the volatiles, the residue was purified by silica gel column flash chromatography eluting with hexanes/EtOAc (0-7 %) to yield the acyl azide **2.01** (3.23 g, 80 %) as colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.76 – 7.67 (m, 4H), 7.49 – 7.36 (m, 6H), 4.18 – 4.07 (m, 1H), 3.75 (d, J = 4.5 Hz, 2H), 2.28 – 2.17 (m, 2H), 2.15 – 2.05 (m, 1H), 1.68 – 1.60 (m, 1H), 1.35 (t, J = 5.8 Hz, 1H), 1.07 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 135.30, 135.29, 132.93, 129.39, 129.36, 127.37, 127.34, 82.51, 69.28, 64.70, 30.64, 29.23, 26.41, 23.34, 18.86. HRMS (ESI⁺) m/z calcd for: C₂₃H₂₇N₂O₃SiNa 444.1714 (M+Na) found 444.17160

Synthesis of (*E*)-3-methoxyacrylamide Intermediate

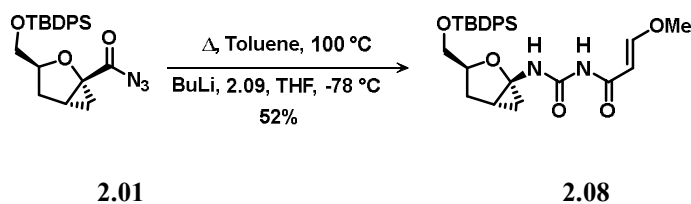


((*E*)-3-methoxyacrylic acid (2.06). A solution of methyl (*E*)-3-methoxyacrylate **2.05** (18.50 mL, 19.95 g, 166.66 mmol) was treated with solution of sodium hydroxide 2.0 M in H₂O (10.67 g, 133.30 mL, 266.65 mmol) stirred for 1 h at room temperature, diluted with ethyl acetate (50 mL) and the layers were separated. The aqueous phase was added with 1.0 M HCl, and extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na₂SO₄ filtered and concentrated. The residue was purified by silica flash chromatography eluting with CH₂Cl₂ containing MeOH(0-5%) to yield acid **2.06** (Rf: 0.32 EtOAc: hexanes, 12.40 g, 73%) as white solid. ¹H NMR (400 MHz, CDCl₃) δ 12.23 (s, 1H), 7.73 (d, J = 12.6 Hz, 1H), 5.20 (d, J = 12.6 Hz, 1H), 3.74 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 173.90, 165.26, 95.46, 57.63.



(*E*)-3-methoxyacrylamide (2.07). A solution of the carboxylic acid **2.06** (12.00 g, 99.56mmol) in CH₂Cl₂ (117 mL) was treated dropwise with thionyl chloride (17.33mL, 235.09 mmol) at r.t, and heated to reflux for 4 hours. The volatiles were removed under reduced pressure. The residue was rapidly dissolved in CH₂Cl₂ (250 mL), and treated with NH₃ bubbles at -20 °C with

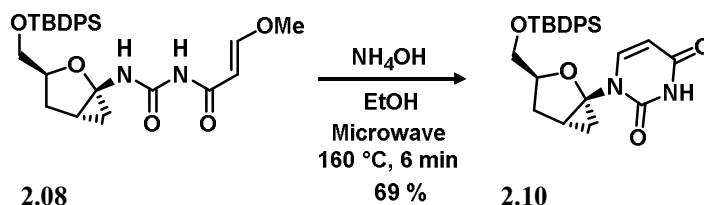
stirring for 30 min. The reaction mixture was allowed to warm to r.t. and the volatiles were removed under reduced pressure. The residue was purified by silica gel flash chromatography eluting with CH₂Cl₂ containing MeOH (0-8%) to yield amide **2.07** as crystalline powder (7.04 g, 70 %) ¹H NMR (300 MHz, DMSO) δ 7.32 (d, *J* = 12.5 Hz, 1H), 7.09 (s, 1H), 6.61 (s, *J* = 11.3 Hz, 1H), 5.28 (d, *J* = 12.5 Hz, 1H), 3.58 (s, 3H). ¹³C NMR (75 MHz, DMSO) δ 167.44, 159.17, 98.99, 57.00.



Freshly prepared lithium-methoxyacrylamide salt: Prepared by the slow addition of *n*-butyl lithium (2.5 M in hexanes, 10.67 mmol, 4.30 mL), to a solution of (*E*)-3-methoxyacrylamide (1.08 g, 10.67 mmol) in dry THF (53 mL) at -78 °C, using a syringe pump over 10 min. The reaction mixture was stirred at -78 °C for 30 min.

(*E*)-N-(((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-yl)carbamoyl)-3-methoxyacrylamide (2.08**)** A solution of acyl azide **2.01** (1.80 g, 4.27mmol) in toluene (47.44 mL) was heated to 100 °C for 3 h and then cooled to -78 °C. A solution of freshly prepared lithium salt from (*E*)-3-methoxyacrylamide **2.09** in THF (53 mL) was added dropwise via cannula at -78 °C to the mixture which was stirred for 1 h. The reaction was quenched by addition of HCl 0.1M. The layers were separated. The aqueous layer was extracted with EtOAc (3 × 70 mL), the combined organic extracts were dried over (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography on

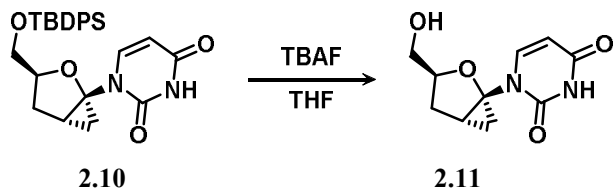
silica gel eluting with hexanes/ EtOAc (0-30%). to yield the acyl urea **2.08** (1.10 g, 52%) as colorless foam. ^1H NMR (400 MHz, CDCl_3) δ 9.90 (s, 1H), 9.55 (s, 1H), 7.66 (dd, J = 6.8, 2.7 Hz, 4H), 7.64 (d, J = 5.9 Hz, 1H), 7.45 – 7.32 (m, 6H), 5.32 (d, J = 12.3 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.81 (dd, J = 10.3, 5.3 Hz, 1H), 3.66 (dd, J = 10.3, 5.5 Hz, 1H), 3.60 (s, 3H), 2.14 – 2.01 (m, 2H), 1.75 – 1.66 (m, 1H), 1.30 – 1.21 (m, 1H), 1.08 (dd, J = 8.3, 5.5 Hz, 1H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 168.01, 163.61, 155.64, 135.71, 133.65, 133.57, 129.76, 127.76, 127.74, 97.68, 79.20, 72.98, 66.21, 57.64, 31.88, 26.93, 21.37, 19.34, 17.80. HRMS (ESI $^+$) m/z calcd for: $\text{C}_{27}\text{H}_{35}\text{N}_2\text{O}_5\text{Si}$ 495.2310 ($\text{M}+\text{H}$) $^+$ found 495.2303. $\text{C}_{27}\text{H}_{34}\text{N}_2\text{O}_5\text{SiNa}$ ($\text{M}+\text{Na}$) $^+$ 517. 2129 found 517.2122



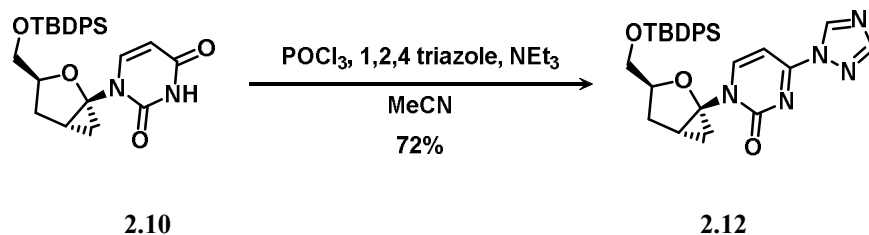
1-((1R,3S,5S)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-

yl)pyrimidine-2,4(1H,3H)-dione (2.10). A solution of the urea **2.08** (200 mg, 0.40 mmol) in ethanol (2.05 mL) was treated with NH_4OH (2 mL) at r.t. The reaction mixture was submitted to microwave conditions at 160 $^\circ\text{C}$ for 6 min. The volatiles were removed under reduced pressure and the residue was purified by silica gel flash chromatography eluting with hexanes/ EtOAc (0-40%). to give the protected uridine analogue **2.10** as colorless foam (120.74 mg, 69%) ^1H NMR (400 MHz, CDCl_3) δ 8.47 (s, 1H), 7.64 (d, J = 7.3 Hz, 4H), 7.39 (ddd, J = 18.6, 9.4, 5.0 Hz, 6H), 7.31 (d, J = 8.1 Hz, 1H), 5.61 (d, J = 8.0 Hz, 1H), 3.98 (td, J = 8.2, 4.3 Hz, 1H), 3.77 (d, J = 4.6 Hz, 2H), 2.40 – 2.30 (m, 1H), 2.11 (dd, J = 12.4, 7.5 Hz, 1H), 1.98 – 1.89 (m,

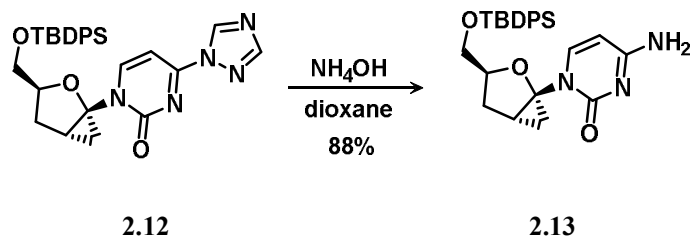
1H), 1.44 (t, $J = 6.2$ Hz, 1H), 1.24 – 1.19 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 163.20, 149.88, 144.98, 135.74, 135.70, 133.61, 133.41, 129.86, 127.81, 127.78, 102.69, 80.69, 79.28, 65.49, 30.86, 27.01, 22.38, 19.43, 18.09. HRMS (ESI^+) m/z calcd for $\text{C}_{26}\text{H}_{34}\text{N}_3\text{O}_4\text{Si}$: 480.23131 ($\text{M}+\text{NH}_4$) $^+$ found 480.23176 $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_4\text{Si}$ 463.2048 ($\text{M}+\text{H}$) $^+$ found 463.2066



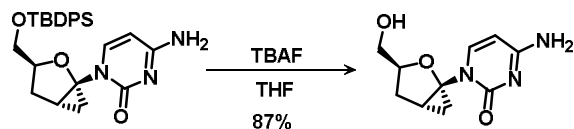
1-((1R,3S,5S)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)pyrimidine-2,4(1H,3H)-dione (2.11). To a stirring solution of **2.10** (162.50 mg, 0.351 mmol) in THF (9.00 mL) tetrabutyl ammonium fluoride (1 M in THF, 0.42 mmol, 0.42 mL) was added dropwise. The mixture was stirred for 1 h. The volatiles were removed under reduced pressure and the residue was purified by silica gel flash chromatography eluting with CH_2Cl_2 containing MeOH (0-5%) to yield the product **2.11** as white foam (65.50 mg, 84 %). ^1H NMR (400 MHz, MeOD) δ 7.68 (d, $J = 8.0$ Hz, 1H), 5.69 (d, $J = 7.9$ Hz, 1H), 4.04 – 3.95 (m, 1H), 3.62 (qd, $J = 11.8, 4.4$ Hz, 2H), 2.33 – 2.22 (m, 1H), 2.11 (dd, $J = 12.3, 7.7$ Hz, 1H), 2.06 – 1.96 (m, 1H), 1.42 (t, $J = 6.2$ Hz, 1H), 1.37 – 1.27 (m, 1H). ^{13}C NMR (75 MHz, MeOD) δ 166.31, 152.36, 147.13, 102.91, 82.08, 80.94, 64.68, 31.14, 23.46, 18.05. HRMS (ESI^+) m/z calcd for: $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_4$ ($\text{M}+\text{H}$) $^+$ 225.0870 found 225.0868.



1-((1R,3S,5S)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-yl)-4-(1H-1,2,4-triazol-1-yl)pyrimidin-2(1H)-one (2.12). To a flask containing 1,2,4-triazole (875.2 mg, 12.67 mmol) and acetonitrile (24 mL) at 0 °C, phosphoryl chloride (332.16 mg, 0.20 mL, 2.12 mmol) was added over a period of 3 minutes using a syringe pump, followed by triethylamine (1.90 mL, 13.69 mmol). The heterogeneous mixture was stirred for 1 h at 0 °C. A solution of pyrimidinone **2.10** (189.10 mg, 0.41 mmol) in acetonitrile (5.10 mL) was transferred via cannula into the mixture, which was allowed to warm to room temperature and stirred for 2.5 h. The reaction was quenched by the addition of saturated aqueous NaHCO₃. The aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried over (Na₂SO₄), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with CH₂Cl₂ containing methanol (0-2%) to give triazole **2.12** (174.00 mg, 83%) as white foam. ¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H), 8.10 (s, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.63 (dd, J = 9.7, 3.7 Hz, 4H), 7.42 – 7.29 (m, 6H), 6.89 (d, J = 7.2 Hz, 1H), 4.15 – 4.02 (m, 1H), 3.83 (d, J = 4.8 Hz, 2H), 2.49 – 2.41 (m, 1H), 2.17 (dd, J = 12.5, 7.6 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.53 – 1.48 (m, 1H), 1.37 – 1.29 (m, 1H), 1.07 – 1.01 (m, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 159.15, 153.67, 150.96, 142.99, 135.18, 135.16, 133.13, 132.91, 129.35, 127.32, 127.30, 94.51, 81.07, 80.89, 65.10, 30.69, 26.52, 22.22, 18.94, 17.94. . HRMS ESI⁺ *m/z* calcd for C₂₈H₃₂N₅O₃Si (M+H)⁺ 514.2269 found 514.2291.



4-Amino-1-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1-yl)pyrimidin-2(1*H*)-one (2.13) To a solution of **2.12** (170.00 mg, 0.33 mmol) in 1,4-dioxane (11.0 mL) ammonium hydroxide (2.25 mL, 43.69 mmol) was added dropwise at room temperature. The solution was stirred for 2 hours. The volatiles were removed under reduced pressure to yield the pyrimidinone **2.13** (Rf: 0.2 CH₂Cl₂: MeOH 5%, 129.90 mg, 85 %), which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.62 (dd, *J* = 6.4, 1.3 Hz, 4H), 7.40 – 7.31 (m, 6H), 7.28 (d, *J* = 7.4 Hz, 1H), 5.68 (d, *J* = 7.3 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.85 – 3.69 (m, 2H), 2.33 – 2.25 (m, 1H), 2.08 (dt, *J* = 22.3, 11.1 Hz, 1H), 1.91 – 1.82 (m, 1H), 1.41 (dd, *J* = 11.8, 5.7 Hz, 1H), 1.20 – 1.11 (m, 1H), 1.03 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 166.19, 156.53, 145.78, 135.64, 135.61, 133.54, 133.32, 129.80, 127.76, 95.78, 80.34, 80.19, 65.73, 31.17, 26.94, 22.20, 19.33, 17.97. HRMS (ESI⁺) *m/z* calcd for C₂₆H₃₂N₃O₃Si (M+H)⁺ 462.2207 found 462.2219.

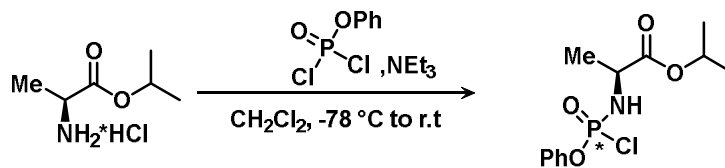


2.13

2.14

4-Amino-1-((1*R*,3*S*,5*S*)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)pyrimidin-

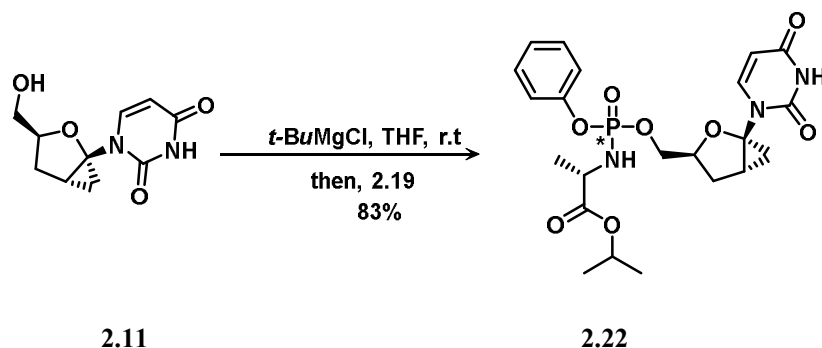
2(1H)-one (2.14) To a stirring solution of **2.13** (83.00 mg, 0.18 mmol) in THF (5.0 mL), 1 M solution of tetrabutylammonium fluoride (0.20 mL 0.2 mmol) was added dropwise. The reaction mixture was stirred for 3h. The volatiles were removed under reduced pressure and the crude was purified by silica gel flash chromatography eluting with CH₂Cl₂/methanol (0-10%) to yield pyrimidinone **2.14** as a white foam (34.80 mg, 0.16 mmol, 87 %). ¹H NMR (300 MHz, MeOD) δ 7.61 (d, *J* = 7.4 Hz, 1H), 5.85 (d, *J* = 7.3 Hz, 1H), 4.05 – 3.93 (m, 1H), 3.69 – 3.60 (m, 1H), 3.51 (dd, *J* = 11.8, 4.6 Hz, 1H), 2.43 – 2.29 (m, 1H), 2.06 (dd, *J* = 12.3, 7.9 Hz, 1H), 1.98 – 1.85 (m, 1H), 1.34 – 1.29 (m, 1H), 1.21 (dd, *J* = 9.8, 6.9 Hz, 1H). ¹³C NMR (75 MHz, MeOD) δ 166.60, 157.30, 146.00, 95.03, 80.80, 80.70, 63.22, 29.59, 22.38, 16.65. HRMS (ESI⁺) *m/z* calcd for C₁₀H₁₄N₃O₃ (M+H)⁺ 224.1030 found 224.1103.



2.19

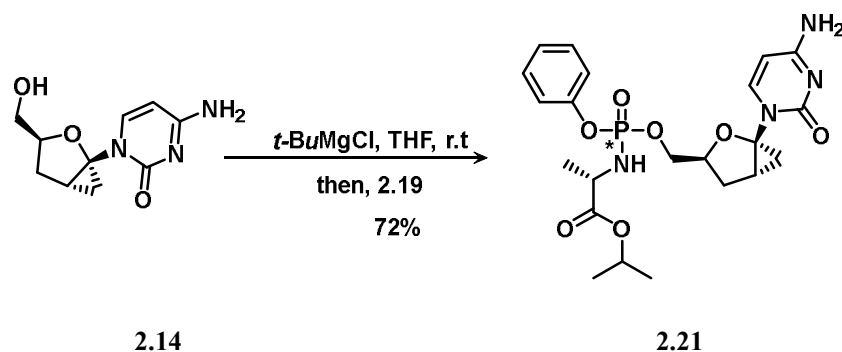
Isopropyl (chloro(phenoxy)phosphoryl)-L-alaninate (2.19) To the alanine-isopropyl ester hydrochloride (300.00 mg, 1.79 mmol) in CH₂Cl₂ (9.0 mL) at -15 °C (Internal temperature) phenyl dichlorophosphate (397.44 mg, 0.28 mL) was added dropwise. After stirring for 15 min, the mixture was cooled to -78 °C and treated with a solution of triethylamine (0.50 mL, 362.19 mg, 3.58 mmol) in CH₂Cl₂ (30 mL) dropwise over a period of 50 min by way of dropping funnel,

keeping the reaction at -78 °C. After total addition, the mixture was stirred for 1 hour, and then allowed to warm to 15 °C (over 1 hour). The volatiles were removed under reduced pressure and the residue was treated with anhydrous diethyl ether (10 mL). The precipitated triethylammonium chloride salt was filtered under argon and washed twice with diethyl ether (5 mL). The combined Et₂O filtrate and washings were evaporated to afford the chloride product **2.19** which was storage up to weeks at -18 °C prior to use.



Isopropyl (((((1*R*,3*S*,5*S*)-1-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(phenoxy)phosphoryl)-L-alaninate (**2.22**). To a solution of uracil **2.11** (14.00 mg, 0.06 mmol) in THF (0.3 mL) a solution of *t*-BuMgCl (1.0M, 0.131mL, 0.13 mmol) was added dropwise at room temperature. As soon as the reagent was added the reaction mixture became heterogeneous. The mixture was stirred for 30 min at r.t, treated dropwise with the chloride **2.19** (0.2M in THF, 0.4 mL, 0.09 mmol) dropwise, stirred for 2 h and quenched with a saturated solution of NH₄Cl was added. The mixture was stirred for 10 minutes. The layers were separated. The aqueous phase was extracted with EtOAc (2x20 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with dichloromethane containing methanol (3-5%) to yield the desired alaninate **2.22** (R_f: 0.5

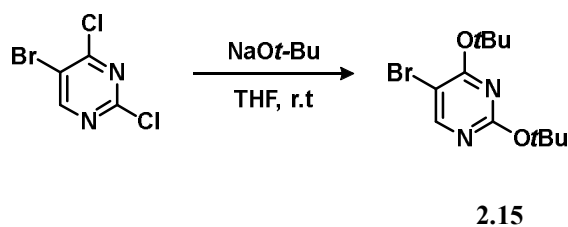
CH₂Cl₂/MeOH 5%) as colorless oil (26.10 mg, 85% as mixture of diastereoisomers 1.6:1 by ³¹P-NMR). Mixture of isomers: ¹H NMR (500 MHz, CDCl₃) δ 8.74 (s, 1H), 7.34 – 7.25 (m, 3H), 7.16 (ddd, J = 21.6, 12.0, 7.9 Hz, 3H), 5.71 – 5.65 (fm, 1H), 5.03 – 4.93 (m, J = 6.2 Hz, 1H), 4.28 – 4.05 (m, 3H), 4.01 – 3.90 (m, 1H), 3.90 – 3.78 (m, 1H), 2.40 – 2.24 (m, 1H), 2.17 – 2.08 (m, 1H), 2.04 – 1.94 (m, 1H), 1.42 – 1.30 (m, 4H), 1.26 – 1.17 (m, 7H). ³¹P NMR (202 MHz, CDCl₃) δ 2.83 (s), 2.70 (s). (1.6:1.0 *d.r.*) respectively ¹³C NMR (126 MHz, CDCl₃) δ 173.16, 173.09, 163.20, 150.95, 150.89, 150.13, 150.00, 144.70, 129.72, 124.99, 124.92, 120.46, 120.42, 120.39, 120.35, 102.90, 79.68, 79.55, 78.93, 78.74, 78.68, 69.31, 67.79, 67.33, 67.29, 50.41, 30.73, 30.37, 22.72, 22.55, 21.82, 21.73, 21.24, 21.19, 21.15, 18.07, 17.97. HRMS (ESI⁺) *m/z* calcd for C₂₂H₂₉N₃O₈P (M+H)⁺ 494.1687 found for 494.1689.



Isopropyl (((((1*R*,3*S*,5*S*)-1-(4-amino-2-oxopyrimidin-1(2*H*)-yl)-2-oxabicyclo[3.1.0]hexan-3-yl)methoxy)(phenoxy)phosphoryl)-*L*-alaninate (2.21) Alaninate **2.21** was synthesized according to the procedure to obtain alaninate **2.20**. To a solution of cytidine **2.14** (16.00 mg, 0.07 mmol in THF (0.4 mL) a solution of *t*-BuMgCl (1.0M, 0.08 mL, 0.08 mmol) was added dropwise at room temperature. After stirred for 30 min, chloride **2.19** was added (0.2 M in THF, 0.4 mL, 0.09 mmol). The residue was purified by silica gel flash chromatography eluting with dichloromethane containing methanol (5-10%) to yield the desired alaninate **2.21** as colorless oil (25.40 mg, 72% as mixture of diastereoisomers 1.8:1 by ³¹P-NMR.). Mixture of

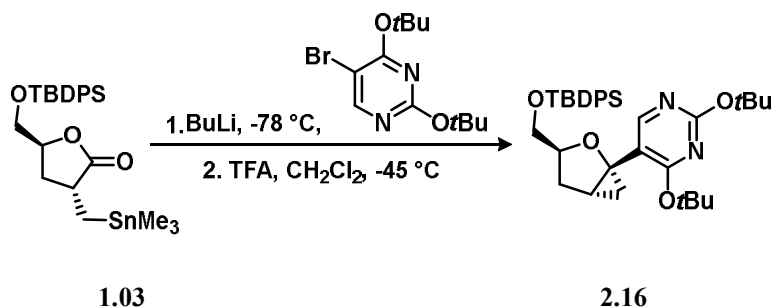
diastereoisomer: ^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.24 (m, 3H(overlap with solvent)), 7.23 – 7.16 (m, 2H), 7.15 – 7.08 (m, 1H), 5.84 (dd, $J = 17.6, 7.3$ Hz, 1H), 4.96 (dt, $J = 12.5, 6.2$ Hz, 1H), 4.31 – 4.15 (m, 2H), 4.15 – 4.03 (m, 1H), 4.03 – 3.77 (m, 2H), 2.34 (d, $J = 5.4$ Hz, 1H), 2.09 (dd, $J = 12.3, 7.5$ Hz, 1H), 2.00 – 1.88 (m, 1H), 1.39 – 1.24 (m, 4H), 1.22 – 1.11 (m, 7H). ^{31}P NMR (121 MHz, CDCl_3) δ 3.65, 3.56 (1:1.8 *d.r.*). ^{13}C NMR (126 MHz, CDCl_3) δ 173.17, 173.11, 166.06, 155.97, 150.93, 150.88, 129.73, 124.96, 120.48, 95.80, 80.93, 80.76, 69.27, 69.21, 50.48, 31.38, 31.18, 22.93, 22.69, 22.14, 21.82, 21.75, 21.07, 18.59. HRMS (ESI $^+$) m/z calcd for $\text{C}_{22}\text{H}_{30}\text{N}_4\text{O}_7\text{P}$ ($\text{M}+\text{H}$) $^+$ 493.1846 found for 493.1863.

3.3.2. Synthesis of 1',2'-methano-2',3'-dideoxypseudouridine **2.17**



5-Bromo-2,4-di-*tert*-butoxypyrimidine (2.15) A solution of the 5-bromo-2,4-dichloropyrimidine (500.00mg, 2.19mmol) in THF (11 mL) was treated dropwise via cannula with a solution of sodium *tert*-butoxide (527.20 mg, 5.49 mmol) in THF (22 mL) at r.t. An immediate change of color was observed from yellow to red. The reaction mixture was stirred for 6 h, quenched with water (50 mL) and extracted with EtOAc (3 x 50 mL). Purification by silica gel flash chromatography eluting with hexanes containing EtOAc (0-4%) to give pyrimidine **2.15** as colorless solid (632.00mg, 92%). ^1H NMR (400 MHz, CDCl_3) δ 8.19 (s, 1H), 1.57 (s, 9 H) 1.54 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 165.68, 162.95, 158.94, 99.55, 83.21,

80.72, 28.32, 28.29. HRMS (ESI⁺) *m/z* calcd for C₁₂H₂₀BrN₂O₂ (M+H)⁺ 303.0703 found 303.0707.

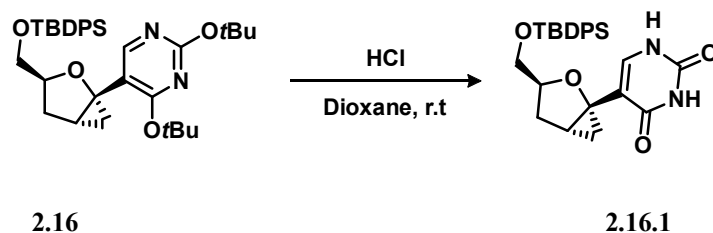


2,4-Di-*tert*-butoxy-5-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-

oxabicyclo[3.1.0]hexan-1-yl)pyrimidine (2.16) To a 2 neck round bottom flask containing a solution of **2.15** (1.71g, 5.65mmol) in THF (56 mL) at -78 °C was added a solution of *n*-BuLi (2.5 M in hexanes, 361.66mg, 5.65mmol 2.26mL) dropwise over 20 minutes using a syringe pump, stirred for 10 min. The mixture was transferred dropwise via cannula over 1 hour to a 3 neck round bottom flask at -78 °C containing a solution of the lactone **1.03** (1.50g, 2.82mmol) in anhydrous THF (56 mL). The mixture was stirred for 2 hours at -72 °C (Internal temperature). The reaction was quenched with pH 7 buffer solution (20 mL). The cold reaction mixture was diluted with EtOAc and the layers were separated, the aqueous layer was extracted with EtOAc (2 X 50 mL). The combined organic layer was dried over (Na₂SO₄), filtered and concentrated under reduced pressure.

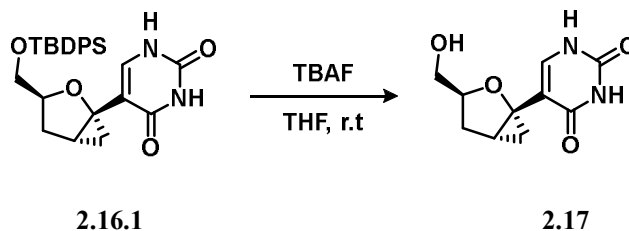
The resulting crude lactol was dissolved in CH₂Cl₂ (141 mL) and cooled to -45 °C. Trifluoroacetic acid (964.20 mg, 0.65 mL, 8.46 mmol) was added dropwise. The reaction internal temperature was maintained below -20 °C. After 20 minutes saturated aqueous solution of NaHCO₃ was added, stirred for 10 minutes. The layers were separated. The aqueous layer

was extracted with CH₂Cl₂ (50 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The reaction residue was purified by silica gel flash chromatography eluting with hexane containing EtOAc (7%) to yield **2.16** (640 mg, 40% over two steps) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 8.35 (s, 1H), 7.70 (d, *J* = 6.8 Hz, 4H), 7.37 (ddd, *J* = 13.4, 9.2, 5.2 Hz, 6H), 4.03 (dq, *J* = 8.7, 5.6 Hz, 1H), 3.83 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.68 (dd, *J* = 10.2, 5.4 Hz, 1H), 2.22 (dd, *J* = 12.1, 7.0 Hz, 1H), 2.10 – 2.04 (m, 1H), 1.79 – 1.69 (m, 1H), 1.62 (s, *J* = 7.8 Hz, 9H), 1.54 (s, 9H), 1.27 – 1.21 (m, 1H), 1.12 (dd, *J* = 10.0, 4.7 Hz, 1H), 1.07 (s, *J* = 7.1 Hz, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 167.80, 163.59, 158.89, 135.75, 133.78, 133.63, 129.74, 127.76, 113.65, 81.53, 80.12, 78.89, 66.54, 65.00, 32.96, 29.85, 28.69, 28.58, 26.97, 21.16, 19.37, 14.69. HRMS (ESI⁺) *m/z* calcd for C₃₄H₄₇N₂O₄Si (M+H)⁺ 575.3300 found 575.3317.



5-((1*R*,3*S*,5*S*)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-oxabicyclo[3.1.0]hexan-1

yl)pyrimidine-2,4(1*H*,3*H*)-dione (2.17) To a stirring solution of imidate **2.16** (15.00 mg, 0.03 mmol) in dioxane (0.3 mL) at room temperature a solution 4.0 M of HCl in dioxanes was added dropwise (0.04 mL, 0.16 mmol), the reaction mixture was stirred for 5 hours. The volatiles were removed under reduced pressure. The residue was employed in the next step without further purification. LR-MS 463.1(M+1), 485.3 (M+23).

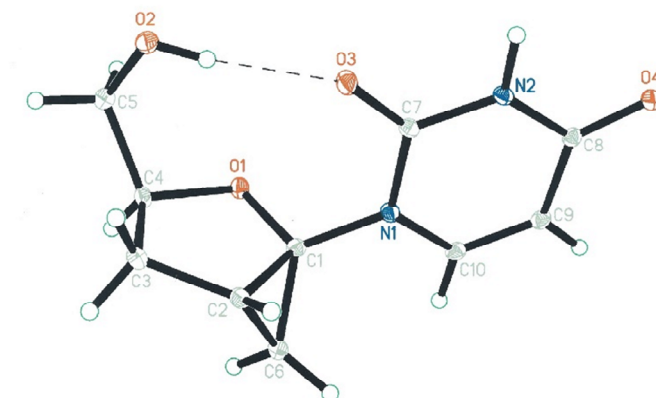
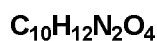
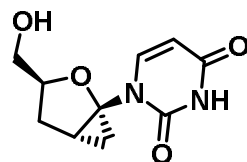


5-((1*R*,3*S*,5*S*)-3-(hydroxymethyl)-2-oxabicyclo[3.1.0]hexan-1-yl)pyrimidine-2,4(1*H*,3*H*)-dione (2.17). To a stirring solution of silyl ether **2.16.1** (15.00 mg, 0.03 mmol) in THF (0.8 mL) at r.t, a solution of tetrabutylammonium fluoride (1 M in THF, 0.04 mmol, 0.04 mL) was added dropwise. The mixture was stirred for 4 hours. The solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography eluting with DCM containing methanol (0-5%) to yield the Pseudouridine **2.17** as colorless oil (6.40 mg, 80%). ¹H NMR (400 MHz, MeOD) δ 7.49 (s, 1H), 4.07 – 3.94 (m, 1H), 3.67 (dd, *J* = 11.7, 3.2 Hz, 1H), 3.50 (dd, *J* = 8.1, 3.6 Hz, 1H), 2.26 – 2.18 (m, 1H), 2.12 (dd, *J* = 12.1, 7.5 Hz, 1H), 1.81 – 1.74 (m, 1H), 1.18 (m, 1H), 1.02 – 0.96 (m, 1H). ¹³C NMR (101 MHz, MeOD) δ 166.05, 141.34, 112.76, 81.36, 81.13, 66.67, 64.59, 49.00, 31.68, 22.87, 15.02. HRMS (ESI⁺) *m/z* calcd for C₁₀H₁₃N₂O₄ (M+H)⁺ 225.0870 found 225.0869.

3.4. X-ray Crystallographic Data

3.4.1. 1',2'-Methano-2',3'-dideoxyuridine 2.11

Table 1. Crystal data and structure refinement for Han506 (2.11)



| | |
|----------------------------------|---|
| Identification code | Han506 |
| Empirical formula | $C_{10}H_{12}N_2O_4$ |
| Formula weight | 224.22 |
| Temperature/K | 296.15 |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| $a/\text{\AA}$ | 7.2034(4) |
| $b/\text{\AA}$ | 7.2040(4) |
| $c/\text{\AA}$ | 19.7752(10) |
| $\alpha/^\circ$ | 90 |
| $\beta/^\circ$ | 90 |
| $\gamma/^\circ$ | 90 |
| Volume/ \AA^3 | 1026.2(1) |
| Z | 4 |
| $\rho_{\text{calc}}/\text{cm}^3$ | 1.4512 |
| μ/mm^{-1} | 0.962 |
| $F(000)$ | 473.8 |
| Crystal size/ mm^3 | $0.32 \times 0.12 \times 0.06$ |
| Radiation | $\text{Cu K}\alpha$ ($\lambda = 1.54178$) |

| | |
|--|---|
| 2 Θ range for data collection/ $^{\circ}$ | 8.94 to 144.22 |
| Index ranges | $-8 \leq h \leq 8, -8 \leq k \leq 8, -24 \leq l \leq 24$ |
| Reflections collected | 41969 |
| Independent reflections | 2010 [$R_{\text{int}} = 0.0248, R_{\text{sigma}} = 0.0074$] |
| Data/restraints/parameters | 2010/0/153 |
| Goodness-of-fit on F^2 | 1.038 |
| Final R indexes [$I \geq 2\sigma(I)$] | $R_1 = 0.0245, wR_2 = 0.0641$ |
| Final R indexes [all data] | $R_1 = 0.0245, wR_2 = 0.0641$ |
| Largest diff. peak/hole / $e \text{ \AA}^{-3}$ | 0.20/-0.15 |
| | 0.07(13) |
| Flack parameter | |

Table 2. Fractional Atomic Coordinates ($\times 104$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 103$) for Han506.

Ueq is defined as 1/3 of of the trace of the orthogonalised UIJ tensor.

| Atom | x | y | z | U(eq) |
|------|------------|-------------|-----------|-----------|
| O1 | 6054.4(11) | 1759.1(11) | 7055.4(4) | 14.53(18) |
| O2 | 9995.3(12) | 1768.9(13) | 6908.5(5) | 19.97(19) |
| O3 | 7951.6(11) | 3200.6(11) | 5816.5(4) | 17.79(19) |
| O4 | 3978.5(11) | 7385.6(11) | 4903.3(4) | 16.20(18) |
| N1 | 4837.1(13) | 2786.5(13) | 6018.2(5) | 13.6(2) |
| N2 | 5902.5(14) | 5247.4(14) | 5361.2(5) | 14.2(2) |
| C1 | 5178.5(15) | 1222.2(15) | 6451.4(5) | 13.3(2) |
| C2 | 5848.1(17) | -628.4(15) | 6225.9(6) | 15.8(2) |
| C3 | 7285.2(17) | -1243.3(17) | 6732.8(6) | 17.6(2) |
| C4 | 7196.6(17) | 228.6(16) | 7299.8(5) | 15.2(2) |
| C5 | 9062.7(17) | 1051.0(17) | 7486.4(6) | 17.0(2) |
| C6 | 3861.4(17) | -376.5(17) | 6477.9(6) | 17.5(2) |
| C7 | 6349.5(16) | 3704.2(16) | 5737.4(5) | 13.7(2) |
| C8 | 4141.6(16) | 5974.9(15) | 5249.8(5) | 13.8(2) |
| C9 | 2656.5(16) | 4970.8(17) | 5572.2(5) | 15.2(2) |
| C10 | 3051.5(16) | 3456.8(16) | 5941.6(6) | 14.5(2) |

Table 3 Anisotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for Han506. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\dots]$.

| Atom | U ₁₁ | U ₂₂ | U ₃₃ | U ₁₂ | U ₁₃ | U ₂₃ |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| O1 | 16.7(4) | 13.8(4) | 13.0(4) | 1.7(3) | -0.7(3) | -0.2(3) |
| O2 | 12.8(4) | 22.0(4) | 25.1(4) | -0.7(4) | 1.2(3) | 6.3(4) |
| O3 | 12.5(4) | 18.7(4) | 22.2(4) | 2.4(3) | 1.8(3) | 6.6(3) |
| O4 | 14.8(4) | 15.2(4) | 18.6(4) | 0.3(3) | -2.3(3) | 3.9(3) |
| N1 | 11.8(5) | 13.8(4) | 15.2(4) | 0.2(4) | 1.3(4) | 2.3(4) |
| N2 | 11.9(5) | 13.8(4) | 16.8(4) | -1.4(4) | 1.1(4) | 3.3(4) |
| C1 | 13.5(5) | 14.2(5) | 12.4(5) | -1.6(4) | 0.8(4) | 1.1(4) |
| C2 | 18.2(6) | 12.7(5) | 16.5(5) | -1.0(4) | -0.2(5) | 0.5(4) |
| C3 | 18.8(6) | 12.4(5) | 21.5(6) | 1.0(5) | -2.0(5) | 1.1(4) |
| C4 | 15.7(6) | 14.7(5) | 15.1(5) | 0.4(5) | -0.6(4) | 4.3(4) |
| C5 | 15.7(6) | 17.5(5) | 17.9(5) | 0.5(5) | -0.9(4) | 0.5(4) |
| C6 | 15.8(6) | 17.2(5) | 19.6(5) | -3.6(5) | -2.1(5) | 4.4(4) |

| | | | | | | |
|-----|---------|---------|---------|---------|---------|---------|
| C7 | 13.8(5) | 13.8(5) | 13.4(5) | -0.7(4) | 1.2(4) | 0.6(4) |
| C8 | 14.7(5) | 13.6(5) | 12.9(5) | 0.3(4) | -1.8(4) | -1.3(4) |
| C9 | 11.1(5) | 17.7(6) | 16.9(5) | 0.3(4) | -0.4(4) | 0.3(4) |
| C10 | 10.9(5) | 18.4(5) | 14.1(5) | -1.9(5) | 0.9(4) | -0.1(4) |

Table 4. Bond Lengths for Han506.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|------|------|------------|------|------|------------|
| O1 | C1 | 1.4052(13) | N2 | C8 | 1.3901(15) |
| O1 | C4 | 1.4582(13) | C1 | C2 | 1.4862(15) |
| O2 | C5 | 1.4230(14) | C1 | C6 | 1.4932(15) |
| O3 | C7 | 1.2198(15) | C2 | C3 | 1.5075(16) |
| O4 | C8 | 1.2313(14) | C2 | C6 | 1.5262(17) |
| N1 | C1 | 1.4367(14) | C3 | C4 | 1.5446(16) |
| N1 | C7 | 1.3902(15) | C4 | C5 | 1.5146(16) |
| N1 | C10 | 1.3822(14) | C8 | C9 | 1.4401(15) |
| N2 | C7 | 1.3758(15) | C9 | C10 | 1.3433(16) |

Table 5. Bond Angles for Han506.

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|------|------|------|------------|------|------|------|------------|
| C4 | O1 | C1 | 109.08(8) | C4 | C3 | C2 | 104.63(9) |
| C7 | N1 | C1 | 118.49(9) | C3 | C4 | O1 | 107.56(8) |
| C10 | N1 | C1 | 119.91(9) | C5 | C4 | O1 | 106.60(9) |
| C10 | N1 | C7 | 121.29(9) | C5 | C4 | C3 | 114.12(10) |
| C8 | N2 | C7 | 127.15(9) | C4 | C5 | O2 | 111.44(9) |
| N1 | C1 | O1 | 111.58(9) | C2 | C6 | C1 | 58.96(7) |
| C2 | C1 | O1 | 110.87(9) | N1 | C7 | O3 | 123.28(10) |
| C2 | C1 | N1 | 125.47(9) | N2 | C7 | O3 | 122.08(10) |
| C6 | C1 | O1 | 117.88(9) | N2 | C7 | N1 | 114.64(10) |
| C6 | C1 | N1 | 121.15(10) | N2 | C8 | O4 | 119.11(10) |
| C6 | C1 | C2 | 61.63(8) | C9 | C8 | O4 | 126.16(11) |
| C3 | C2 | C1 | 106.68(9) | C9 | C8 | N2 | 114.73(10) |
| C6 | C2 | C1 | 59.41(7) | C10 | C9 | C8 | 119.42(10) |
| C6 | C2 | C3 | 117.50(10) | C9 | C10 | N1 | 122.71(10) |

Table 6. Hydrogen Bonds for han506.

| D | H | A | d(D-H)/Å | d(H-A)/Å | d(D-A)/Å | D-H-A/° |
|----|-----|-----|-----------|-----------|------------|-----------|
| N2 | H2a | O41 | 0.883(16) | 1.972(16) | 2.8444(13) | 169.4(14) |
| O2 | H2 | O3 | 0.842(18) | 2.003(18) | 2.8096(12) | 160.1(15) |

$$11/2+X,3/2-Y,1-Z$$

Table 7 Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for han506.

| Atom | <i>x</i> | <i>y</i> | <i>z</i> | U(eq) |
|------|------------|-------------|-----------|---------|
| H2b | 6068.4(17) | -847.2(15) | 5743.4(6) | 18.9(3) |
| H3a | 6993.2(17) | -2466.7(17) | 6907.9(6) | 21.1(3) |
| H3b | 8509.8(17) | -1275.8(17) | 6529.1(6) | 21.1(3) |
| H4 | 6621.6(17) | -315.4(16) | 7702.9(5) | 18.2(3) |
| H5a | 9826.0(17) | 101.8(17) | 7695.6(6) | 20.4(3) |
| H5b | 8883.5(17) | 2039.0(17) | 7813.2(6) | 20.4(3) |
| H6a | 3547.3(17) | -878.9(17) | 6918.4(6) | 21.0(3) |
| H6b | 2868.4(17) | -416.2(17) | 6146.9(6) | 21.0(3) |
| H9 | 1434.7(16) | 5367.2(17) | 5525.0(5) | 18.3(3) |
| H10 | 2083.7(16) | 2833.8(16) | 6154.6(6) | 17.4(3) |
| H2a | 6860(20) | 5920(20) | 5226(7) | 20(4) |
| H2 | 9190(20) | 2260(20) | 6656(8) | 25(4) |

Experimental

Single crystals of $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4$ [han506] were [1]. A suitable crystal was selected and [1] on a Bruker Smart APEX diffractometer. The crystal was kept at 296.15 K during data collection. Using Olex2 [1], the structure was solved with the olex2.solve [2] structure solution program using Charge Flipping and refined with the XH [3] refinement package using CGLS minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
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3. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2015). Acta Cryst. A71, 59-75.

Crystal structure determination of [han506]

Crystal Data for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4$ ($M = 224.22$ g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 7.2034(4)$ Å, $b = 7.2040(4)$ Å, $c = 19.7752(10)$ Å, $V = 1026.2(1)$ Å³, $Z = 4$, $T = 296.15$ K, $\mu(\text{Cu K}\alpha) = 0.962$ mm⁻¹, $D_{\text{calc}} = 1.4512$ g/cm³, 41969 reflections measured ($8.94^\circ \leq 2\theta \leq 144.22^\circ$), 2010 unique ($R_{\text{int}} = 0.0248$, $R_{\text{sigma}} = 0.0074$) which were used in all calculations. The final R_1 was 0.0245 ($I \geq 2\sigma(I)$) and wR_2 was 0.0641 (all data).

Refinement model description

Number of restraints - 0, number of constraints - 17.

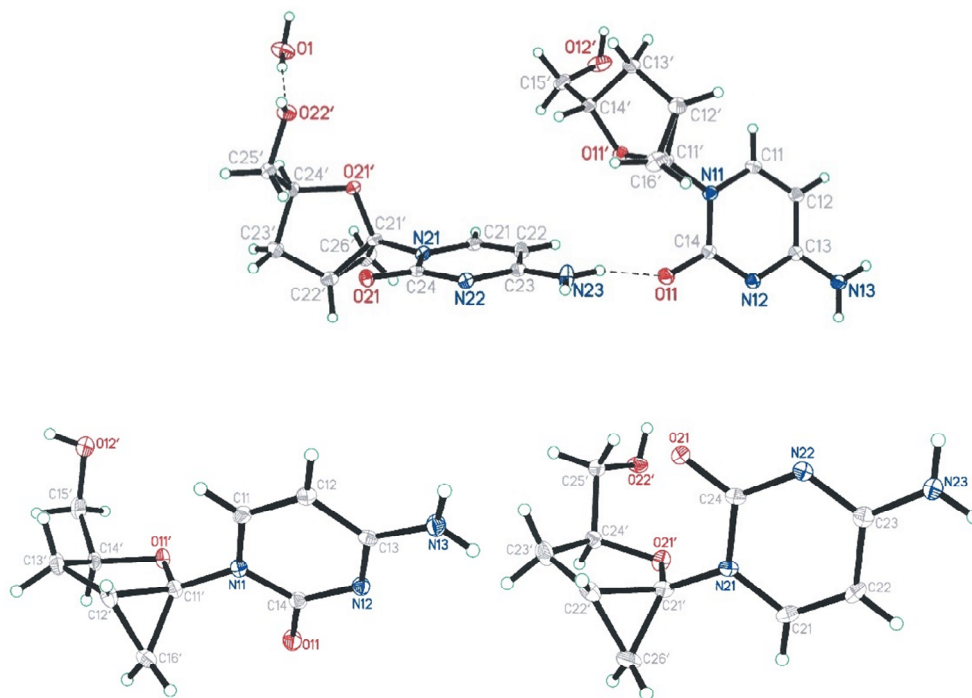
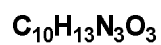
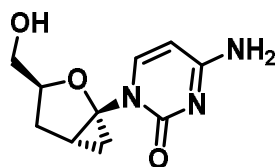
Details:

1. Fixed UisoAt 1.2 times of: All C(H) groups, All C(H,H) groups
- 2.a Ternary CH refined with riding coordinates: C2(H2b), C4(H4)
- 2.b Secondary CH2 refined with riding coordinates: C3(H3a,H3b), C5(H5a,H5b), C6(H6a,H6b)
- 2.c Aromatic/amide H refined with riding coordinates: C9(H9), C10(H10)

This report has been created with Olex2, compiled on 2017.08.10 svn.r3458 for OlexSys. Please [let us know](#) if there are any errors or if you would like to have additional features.

3.4.2. 1',2'-Methano-2',3'-dideoxycytidine 2.14

Table 1. Crystal data and structure refinement for Han517 (2.14)



| | |
|--|---|
| Identification code | Han517 |
| Empirical formula | C ₂₀ H ₂₈ N ₆ O ₇ |
| Formula weight | 464.48 |
| Temperature/K | 100.15 |
| Crystal system | Orthorhombic |
| Space group | P2 ₁ 2 ₁ 2 ₁ |
| a/Å | 8.3659(2) |
| b/Å | 10.2379(3) |
| c/Å | 24.7767(7) |
| $\alpha/^\circ$ | 90 |
| $\beta/^\circ$ | 90 |
| $\gamma/^\circ$ | 90 |
| Volume/Å ³ | 2122.11(10) |
| Z | 4 |
| $\rho_{\text{calc}}/\text{cm}^3$ | 1.4537 |
| μ/mm^{-1} | 0.939 |
| F(000) | 987.6 |
| Crystal size/mm ³ | 0.22 × 0.2 × 0.08 |
| Radiation | Cu K α (λ = 1.54178) |
| 2 Θ range for data collection/ $^\circ$ | 7.14 to 144.56 |
| Index ranges | -10 ≤ h ≤ 10, -12 ≤ k ≤ 12, -30 ≤ l ≤ 30 |
| Reflections collected | 88391 |
| Independent reflections | 4166 [R _{int} = 0.0219, R _{sigma} = 0.0063] |
| Data/restraints/parameters | 4166/0/165 |
| Goodness-of-fit on F ² | 1.035 |
| Final R indexes [I ≥ 2 σ (I)] | R ₁ = 0.0424, wR ₂ = 0.1006 |
| Final R indexes [all data] | R ₁ = 0.0424, wR ₂ = 0.1022 |
| Largest diff. peak/hole / e Å ⁻³ | 0.52/-0.35 |
| Flack parameter | 0.1(2) |

Table 2. Fractional Atomic Coordinates (×10⁴) and Equivalent Isotropic Displacement Parameters (Å²×10³) for han517.

U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{ij} tensor.

| Atom | x | y | z | U(eq) |
|------|------------|------------|-----------|---------|
| O1 | -248(2) | 5016.4(17) | 5577.0(7) | 24.4(4) |
| O11 | 8139.9(18) | 3117.3(15) | 2329.5(6) | 17.4(3) |
| O11' | 4388.4(17) | 3204.7(14) | 2540.1(6) | 14.9(3) |
| O12' | 1120(2) | 2199.8(17) | 2635.4(7) | 26.0(4) |
| N11 | 6001(2) | 2932.7(17) | 1766.4(6) | 13.3(3) |
| N12 | 8511(2) | 1959.5(17) | 1556.9(7) | 13.1(4) |
| N13 | 8802(2) | 858.7(18) | 759.1(7) | 16.1(4) |
| C11 | 5319(3) | 2373.9(19) | 1319.3(8) | 14.1(4) |
| C11' | 5077(2) | 3818(2) | 2088.8(8) | 14.4(4) |
| C12 | 6201(3) | 1648(2) | 979.7(8) | 14.8(4) |

| | | | | |
|------|------------|------------|-----------|---------|
| C12' | 3942(3) | 4801(2) | 1854.1(8) | 18.0(4) |
| C13 | 7859(2) | 1494.0(19) | 1103.1(8) | 12.1(4) |
| C13' | 2467(3) | 4725(2) | 2207.2(8) | 17.3(4) |
| C14 | 7597(2) | 2676.3(19) | 1898.2(8) | 12.4(4) |
| C14' | 3051(2) | 3996(2) | 2712.3(8) | 16.1(4) |
| C15' | 1831(3) | 3134(2) | 2988.0(9) | 19.9(4) |
| C16' | 5504(3) | 5232(2) | 2122.1(9) | 21.3(5) |
| O21 | 7187.1(16) | 5828.5(13) | 4914.7(5) | 12.9(3) |
| O21' | 4073.7(17) | 4334.2(14) | 5128.8(6) | 15.3(3) |
| O22' | 2379.4(18) | 6612.8(14) | 5370.8(6) | 16.3(3) |
| N21 | 6288(2) | 3894.7(16) | 4575.4(6) | 11.9(3) |
| N22 | 7704(2) | 5413.5(16) | 4032.0(7) | 12.1(3) |
| N23 | 8073(2) | 5019(2) | 3135.0(8) | 20.3(4) |
| C21 | 6071(3) | 3083(2) | 4137.6(8) | 14.2(4) |
| C21' | 5500(2) | 3628(2) | 5078.7(8) | 12.5(4) |
| C22 | 6658(2) | 3404(2) | 3647.2(8) | 14.8(4) |
| C22' | 6323(3) | 3507(2) | 5606.0(8) | 15.9(4) |
| C23 | 7489(2) | 4631.4(19) | 3602.9(8) | 13.3(4) |
| C23' | 5385(3) | 4325(2) | 6000.6(9) | 18.5(4) |
| C24 | 7074(2) | 5089.0(18) | 4515.5(7) | 10.6(4) |
| C24' | 3919(3) | 4802(2) | 5681.7(8) | 13.7(4) |
| C25' | 3788(2) | 6277(2) | 5666.6(8) | 14.0(4) |
| C26' | 5559(3) | 2313(2) | 5340.8(9) | 18.4(4) |

Table 3. Bond Lengths for han517.

| Atom | Atom | Length/Å | Atom | Atom | Length/Å |
|------|------|----------|------|------|----------|
| O11 | C14 | 1.246(2) | O21 | C24 | 1.249(2) |
| O11' | C11' | 1.405(2) | O21' | C21' | 1.401(2) |
| O11' | C14' | 1.446(2) | O21' | C24' | 1.457(2) |
| O12' | C15' | 1.425(3) | O22' | C25' | 1.429(2) |
| N11 | C11 | 1.371(3) | N21 | C21 | 1.378(3) |
| N11 | C11' | 1.434(3) | N21 | C21' | 1.437(3) |
| N11 | C14 | 1.399(3) | N21 | C24 | 1.396(2) |
| N12 | C13 | 1.337(3) | N22 | C23 | 1.343(3) |
| N12 | C14 | 1.355(3) | N22 | C24 | 1.350(2) |
| N13 | C13 | 1.331(3) | N23 | C23 | 1.319(3) |
| C11 | C12 | 1.343(3) | C21 | C22 | 1.351(3) |
| C11' | C12' | 1.501(3) | C21' | C22' | 1.482(3) |
| C11' | C16' | 1.494(3) | C21' | C26' | 1.496(3) |
| C12 | C13 | 1.430(3) | C22 | C23 | 1.441(3) |
| C12' | C13' | 1.515(3) | C22' | C23' | 1.508(3) |
| C12' | C16' | 1.531(3) | C22' | C26' | 1.528(3) |
| C13' | C14' | 1.537(3) | C23' | C24' | 1.539(3) |
| C14' | C15' | 1.512(3) | C24' | C25' | 1.514(3) |

Table 4. Bond Angles for han517.

| Atom | Atom | Atom | Angle/° | Atom | Atom | Atom | Angle/° |
|------|------|------|------------|------|------|------|------------|
| C14' | O11' | C11' | 107.55(15) | C24' | O21' | C21' | F |
| C11' | N11 | C11 | 119.27(17) | C21' | N21 | C21 | 120.56(16) |
| C14 | N11 | C11 | 120.50(17) | C24 | N21 | C21 | 120.42(16) |
| C14 | N11 | C11' | 120.20(17) | C24 | N21 | C21' | 118.32(16) |
| C14 | N12 | C13 | 119.20(17) | C24 | N22 | C23 | 120.21(17) |
| C12 | C11 | N11 | 120.52(19) | C22 | C21 | N21 | 120.90(19) |
| N11 | C11' | O11' | 112.46(17) | N21 | C21' | O21' | 111.70(16) |
| C12' | C11' | O11' | 110.40(17) | C22' | C21' | O21' | 111.16(16) |
| C12' | C11' | N11 | 123.29(17) | C22' | C21' | N21 | 124.61(17) |
| C16' | C11' | O11' | 119.14(18) | C26' | C21' | O21' | 117.02(17) |
| C16' | C11' | N11 | 120.93(18) | C26' | C21' | N21 | 122.18(17) |
| C16' | C11' | C12' | 61.49(14) | C26' | C21' | C22' | 61.74(14) |
| C13 | C12 | C11 | 117.41(19) | C23 | C22 | C21 | 117.11(19) |
| C13' | C12' | C11' | 104.90(17) | C23' | C22' | C21' | 106.45(17) |
| C16' | C12' | C11' | 59.03(14) | C26' | C22' | C21' | 59.58(14) |
| C16' | C12' | C13' | 117.36(18) | C26' | C22' | C23' | 120.36(19) |
| N13 | C13 | N12 | 118.12(19) | N23 | C23 | N22 | 117.84(19) |
| C12 | C13 | N12 | 122.41(18) | C22 | C23 | N22 | 121.65(18) |
| C12 | C13 | N13 | 119.47(19) | C22 | C23 | N23 | 120.51(19) |
| C14' | C13' | C12' | 103.67(17) | C24' | C23' | C22' | 104.97(17) |
| N11 | C14 | O11 | 118.67(18) | N21 | C24 | O21 | 118.85(17) |
| N12 | C14 | O11 | 121.74(18) | N22 | C24 | O21 | 121.58(17) |
| N12 | C14 | N11 | 119.59(17) | N22 | C24 | N21 | 119.57(16) |
| C13' | C14' | O11' | 106.13(16) | C23' | C24' | O21' | 107.92(16) |
| C15' | C14' | O11' | 109.14(17) | C25' | C24' | O21' | 108.13(15) |
| C15' | C14' | C13' | 115.90(18) | C25' | C24' | C23' | 112.80(17) |
| C14' | C15' | O12' | 113.36(18) | C24' | C25' | O22' | 108.20(16) |
| C12' | C16' | C11' | 59.48(14) | C22' | C26' | C21' | 58.68(13) |

Table 5. Hydrogen Bonds for han517.

| D | H | A | d(D-H)/Å | d(H-A)/Å | d(D-A)/Å | D-H-A/° |
|------|------|------------------|----------|----------|----------|---------|
| O1 | H1a | O21 ¹ | 0.94(6) | 1.91(6) | 2.827(2) | 168(5) |
| O1 | H1b | O22' | 0.90(5) | 1.90(5) | 2.786(2) | 168(4) |
| O12' | H12' | O11 ¹ | 0.90(4) | 1.92(4) | 2.770(2) | 156(3) |
| O22' | H22' | O21 ² | 0.93(3) | 1.81(4) | 2.718(2) | 164(3) |
| N23 | H23b | O11 | 0.89(3) | 1.93(4) | 2.788(3) | 162(3) |

$$^1\text{-}1+\text{X},+\text{Y},+\text{Z}; ^2\text{-}1/2+\text{X},3/2\text{-}\text{Y},1\text{-}\text{Z}$$

Table 6. Hydrogen Atom Coordinates ($\text{\AA} \times 10^4$) and Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for han517.

| Atom | x | y | z | U(eq) |
|------|-----------|------------|-----------|---------|
| H1a | -1170(70) | 5320(50) | 5400(20) | 101(17) |
| H1b | 560(50) | 5530(40) | 5462(16) | 65(12) |
| H12' | 290(40) | 2510(30) | 2442(13) | 44(9) |
| H13a | 9800(40) | 790(30) | 848(12) | 34(8) |
| H13b | 8460(40) | 690(30) | 414(12) | 33(8) |
| H11 | 4213(3) | 2501.0(19) | 1249.1(8) | 16.9(5) |
| H12 | 5741(3) | 1252(2) | 669.7(8) | 17.8(5) |
| H12a | 3822(3) | 4870(2) | 1453.5(8) | 21.6(5) |
| H13c | 2073(3) | 5608(2) | 2300.6(8) | 20.7(5) |
| H13d | 1600(3) | 4236(2) | 2024.9(8) | 20.7(5) |
| H14' | 3445(2) | 4654(2) | 2979.4(8) | 19.3(5) |
| H15a | 980(3) | 3691(2) | 3142.9(9) | 23.8(5) |
| H15b | 2356(3) | 2667(2) | 3289.7(9) | 23.8(5) |
| H16a | 5435(3) | 5662(2) | 2479.2(9) | 25.5(5) |
| H16b | 6373(3) | 5555(2) | 1885.9(9) | 25.5(5) |
| H22' | 2510(40) | 7470(30) | 5250(13) | 46(9) |
| H23a | 8590(40) | 5790(30) | 3101(11) | 30(8) |
| H23b | 7920(40) | 4520(30) | 2849(14) | 41(9) |
| H21 | 5502(3) | 2287(2) | 4181.3(8) | 17.0(5) |
| H22 | 6529(2) | 2844(2) | 3344.6(8) | 17.8(5) |
| H22a | 7516(3) | 3567(2) | 5613.1(8) | 19.1(5) |
| H23c | 5052(3) | 3796(2) | 6315.7(9) | 22.2(5) |
| H23d | 6031(3) | 5073(2) | 6129.2(9) | 22.2(5) |
| H24' | 2928(3) | 4429(2) | 5846.1(8) | 16.4(5) |
| H25a | 4742(2) | 6656(2) | 5489.4(8) | 16.8(5) |
| H25b | 3721(2) | 6628(2) | 6038.2(8) | 16.8(5) |
| H26a | 4561(3) | 1966(2) | 5500.4(9) | 22.1(5) |
| H26b | 6277(3) | 1647(2) | 5182.3(9) | 22.1(5) |

Experimental

Single crystals of $\text{C}_{20}\text{H}_{28}\text{N}_6\text{O}_7$ [han517] were [1]. A suitable crystal was selected and [1] on a **Bruker Smart APEX** diffractometer. The crystal was kept at 100.15 K during data collection. Using Olex2 [1], the structure was solved with the SIR2004 [2] structure solution program using Direct Methods and refined with the olex2.refine [3] refinement package using Gauss-Newton minimisation.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J., Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Burla, M.C., Caliendo, R., Camalli, M., Carrozzini, B., Cascarano, G.L., De Caro, L., Giacovazzo, C., Polidori, G., Siliqi, D., Spagna, R. (2007). J. Appl. Cryst. 40, 609-613.
3. Bourhis, L.J., Dolomanov, O.V., Gildea, R.J., Howard, J.A.K., Puschmann, H. (2015). Acta Cryst. A71, 59-75.

Crystal structure determination of [han517]

Crystal Data for $C_{20}H_{28}N_6O_7$ ($M = 464.48$ g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.3659(2)$ Å, $b = 10.2379(3)$ Å, $c = 24.7767(7)$ Å, $V = 2122.11(10)$ Å³, $Z = 4$, $T = 100.15$ K, $\mu(\text{Cu K}\alpha) = 0.939$ mm⁻¹, $D_{\text{calc}} = 1.4537$ g/cm³, 88391 reflections measured ($7.14^\circ \leq 2\Theta \leq 144.56^\circ$), 4166 unique ($R_{\text{int}} = 0.0219$, $R_{\text{sigma}} = 0.0063$) which were used in all calculations. The final R_1 was 0.0424 ($I \geq 2u(I)$) and wR_2 was 0.1022 (all data).

Refinement model description

Number of restraints - 0, number of constraints - 34.

Details:

1. Fixed Uiso At 1.2 times of: All C(H) groups, All C(H,H) groups
- 2.a Ternary CH refined with riding coordinates: C12'(H12a), C14'(H14'), C22'(H22a), C24'(H24')
- 2.b Secondary CH2 refined with riding coordinates: C13'(H13c,H13d), C15'(H15a,H15b), C16'(H16a,H16b), C23'(H23c,H23d), C25'(H25a,H25b), C26'(H26a,H26b)
- 2.c Aromatic/amide H refined with riding coordinates: C11(H11), C12(H12), C21(H21), C22(H22)

4.0 References

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